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Assessment of Drug Utilization Patterns, Medication Compliance and Physician Adherence to Lipid and Safety Monitoring Guidelines among Patients on Lipid-Lowering Drugs in the Texas Medicaid System

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Assessment of Drug Utilization Patterns, Medication Compliance and Physician Adherence to Lipid and Safety Monitoring Guidelines among Patients on Lipid-Lowering Drugs in the Texas Medicaid System

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Dedication

This dissertation is dedicated to my loving grandmother *Daulat*,

whose values and unconditional love have touched the hearts of many

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Assessment of Drug Utilization Patterns, Medication Compliance and Physician Adherence to Lipid and Safety Monitoring Guidelines among Patients on Lipid-Lowering Drugs in the Texas Medicaid System

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Hyperlipidemia plays a central role in the development of atherosclerotic plaque that impairs arterial blood flow leading to arterial obstruction and myocardial infarction in coronary vessels. The management of hyperlipidemia is crucial in the prevention of coronary heart disease (CHD). Primary, secondary, and angiographic trials have demonstrated the beneficial effects of lipid-lowering drugs, especially statins, in the reduction of CHD associated mortality and morbidity.

The purpose of the study was to evaluate statin utilization patterns, medication compliance, and lipid and safety monitoring of patients on statin drug therapy in the

Texas Medicaid system. The study was a retrospective cohort analysis using the Texas Medicaid database. The study population included patients who were new statin users between the ages of 21 and 64 years and were eligible for Texas Medicaid benefits between September 1, 1998 to August 31, 2003.

Of the total (N = 7,440) patients, 65.2% were females and the mean age of all patients was 49.7 years (S.D. = 9.4 years). Non-Hispanic whites (42.7%), Hispanics (32.7%), and non-Hispanic blacks (22.5%) formed the majority of the ethnic categories. The most commonly prescribed statins, based on the total number of prescription claims for the two-year follow-up period, were Lipitor® (57.1%), Zocor® (23.2%) and Pravachol® (14.2%). Compliance was measured using the medication possession ratio (MPR) and persistence. The mean MPR was 0.7 and at the end of 310 days, only 50 percent of the patients were still persistent with their therapy. The cumulative probability of being persistent with therapy at the end of the two-year period was 0.41. Within three months prior to the start of therapy, less than half (42.5%) of the patients had their LDL levels monitored. Only 15.6 percent and 9.7 percent of the patients had LDL tests and liver function tests (LFTs) within three months since the start of therapy.

The study showed the lack of adherence to statin drugs and lack of monitoring of the response to the drugs, as well as associated adverse events, both of which could cost the Medicaid system valuable dollars in the long run. Steps need to be taken to promote adherence and monitoring in order to reduce the risk and the long-term costs associated with CHD.

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CHAPTER 1

INTRODUCTION AND LITERATURE REVIEW

Cardiovascular diseases (CVD) are the leading causes of mortality and morbidity among men and women from developed countries.[1] According to the American Heart Association, in the year 2001, CVDs were associated with 38.5 percent of all deaths (1 in every 2.6 deaths) in the United States (U.S.), claiming 1,408,000 lives.[2] Coronary heart disease (CHD), also referred to as coronary artery disease, accounts for about half of all cardiovascular-related deaths in the U.S.[3] A total of 13 million people suffer from CHD, of which, 7.1 million suffer from myocardial infarction (MI) and 6.4 million suffer from angina pectoris. CHD was responsible for one in every five deaths in the U.S in the year 2002. The estimated U.S. annual cost of CHD in 2005, including both direct and indirect costs was $142.1 billion.

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[1] McKenney JM. Pharmacotherapy of dyslipidemia. *Cardiovascular Drugs & Therapy.* 2001;15(5):413-422.

[2] American Heart Association. Heart Disease and Stroke Statistics - 2005 Update. *American Heart Association*. Available at: http://www.americanheart.org/presenter.jhtml?identifier=1928. Accessed January 15, 2005.

[3] American Heart Association. Heart Disease and Stroke Statistics - 2005 Update. *American Heart Association*. Available at: http://www.americanheart.org/presenter.jhtml?identifier=1928. Accessed January 15, 2005.

Moreover, CHD is the leading cause of "premature, permanent disability in the U.S. labor force, accounting for 19 percent of disability allowances by the Social Security Administration."[4]

The epidemiological literature has documented the association between elevated cholesterol level (hyperlipidemia) and the increased risk for CHD.[5,6] A substantial number of U.S. adults are hyperlipidemic. Based on the data from NHANES III, overall 50.7 million (28.2 percent) of U.S. adults $\geq$ 20 years are eligible for treatment based on the Adult Treatment Panel (ATP) II guidelines.[7] The management of hyperlipidemia is crucial in preventing the occurrence of CHD. However, under-diagnosis and under-treatment of this disorder prevails in clinical practice.[8]

The National Cholesterol Education Program (NCEP) of the National Institute of Health provides updates and recommendations for cholesterol testing and management.

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[4] American Heart Association. Heart Disease and Stroke Statistics - 2005 Update. *American Heart Association*. Available at: http://www.americanheart.org/presenter.jhtml?identifier=1928. Accessed January 15, 2005.

[5] Kannel WB, Castelli WP, Gordon T, et al. Serum cholesterol, lipoproteins, and the risk of coronary heart disease. The Framingham study. *Annals of Internal Medicine.* 1971;74(1):1-12.

[6] Stamler J, Wentworth D, Neaton JD. Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). *Journal of the American Medical Association.* 1986;256(20):2823-2828.

[7] Hoerger TJ, Bala MV, Bray JW, et al. Treatment patterns and distribution of low-density lipoprotein cholesterol levels in treatment-eligible United States adults. *American Journal of Cardiology.* 1998;82(1):61-65.

[8] Lai L, Poblet M, Bello C. Are patients with hyperlipidemia being treated? Investigation of cholesterol treatment practices in an HMO primary care setting. *Southern Medical Journal.* 2000;93(3):283-286.

The lipid-lowering agents, statins, are recommended as the first line of drug therapy in the treatment of hyperlipidemia.[9] Clinical trials have demonstrated the beneficial effects of statins in reducing cholesterol levels as well as CHD mortality and morbidity.[10,11,12] Despite, these beneficial effects, the use of statins for lipid management remains sub-optimal. Moreover, the compliance to statin therapy is low.[13]

Given the expense and the life-long treatment of the condition, it is important to understand the treatment and monitoring of hyperlipidemia. There has been no published study on the management of hyperlipidemia and adherence to lipid and safety monitoring guidelines in the Texas Medicaid program. Moreover, limited data exists on the management of hyperlipidemia among women and minority populations such as Hispanics and African-Americans. This study aims to understand treatment patterns, adherence to lipid and safety monitoring guidelines and compliance to statin drug

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[9] Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *Journal of the American Medical Association.* 2001;285(19):2486-2497.

[10] Shepherd J, Cobbe S, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *New England Journal of Medicine.* 1995;333(20):1301-1307.

[11] Kjekshus J, Pedersen TR. Reducing the Risk of Coronary Events: Evidence from the Scandinavian Simvastatin Survival Study (4S). *American Journal of Cardiology.* 1995;76(1):64C-68C.

[12] Sacks FM, Moye LA, Davis BR, et al. Relationship between plasma LDL concentrations during treatment with pravastatin and recurrent coronary events in the Cholesterol and Recurrent Events Trial. *Circulation.* 1998;97(15):1446-1452.

[13] Andrade SE, Walker AM, Gottolieb LK, et al. Discontinuation of antihyperlipidemic drugs-do rates reported in clinical trials reflect rates in primary care settings? *New England Journal of Medicine.* 1995;332(17):1125-1131.

regimen among hyperlipidemic patients enrolled in the Texas Medicaid program.

This chapter is divided into the following nine sections:

1. Background on hyperlipidemia;
2. Clinical evidence of lipid-lowering with anti-hyperlipidemic drugs and its effect on CHD;
3. Compliance with lipid-lowering therapy;
4. Lipid management in primary care settings and in special populations;
5. Impact of physician specialty on management of hyperlipidemia and CHD;
6. Pharmacoeconomic evaluations of lipid-lowering therapy;
7. Use of claims databases in health outcomes research;
8. Texas Medicaid database and cardiovascular disease in Texas; and
9. Goals and objectives of the study.

SECTION I

BACKGROUND ON HYPERLIPIDEMIA

This section presents information on: the epidemiology of hyperlipidemia in the U.S. population; the process of atherosclerosis including the role of lipids and lipoproteins in the development of CHD; the risk factors associated with hyperlipidemia; the guidelines for its treatment; and finally, the dietary and pharmacological management of the disease.

Definition of Hyperlipidemia and Its Association with CHD

Hyperlipidemia (also referred to as dyslipidemia or hypercholesterolemia), is defined as elevated plasma cholesterol levels. Grundy et al. defined hyperlipidemia as "cholesterol concentration associated with significantly increased risk for coronary heart disease."[14] There are five major types of lipids in the blood plasma: cholesterol, cholesteryl esters, phospholipids, triglycerides and unesterified fatty acids. Lipoproteins are responsible for the transport of lipids, mainly triglycerides and cholesterol, through the plasma. The four main classes of lipoproteins include high-density lipoprotein (HDL), low-density lipoprotein (LDL), very low-density lipoprotein (VLDL) and

[14] Grundy SM. Cholesterol and coronary heart disease: A new era. *Journal of the American Medical Association.* 1986;256(20):2849-2858.

chylomicrons.[15] LDL makes up about 60-70 percent of the total serum cholesterol and is the primary target of cholesterol lowering therapy as recognized by the National Cholesterol Education Panel (NCEP).[16] LDL cholesterol plays an important role in the occurrence of CHD.

The epidemiological literature has documented the association between elevated cholesterol level (hyperlipidemia) and the increased risk for CHD. Studies such as the Framingham Heart Study,[17] the Multiple Risk Factor Intervention Trial (MRFIT),[18] and the Lipid Research Clinics Primary Prevention Trial (LRCPPT)[19,20] show a direct association between the prevalence of high cholesterol and the occurrence of CHD in subjects initially free of CHD.

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[15] Patsch JR. *An introduction to the biochemistry and biology of blood lipids and lipoproteins*. Berlin Heidelberg: Springer-Verlag; 1994.

[16] Grundy SM, Becker DM, Clark L, et al. Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *Journal of the American Medical Association.* 2001;285(19):2486-2497.

[17] Kannel WB, Castelli WP, Gordon T, et al. Serum cholesterol, lipoproteins, and the risk of coronary heart disease. The Framingham study. *Annals of Internal Medicine.* 1971;74(1):1-12.

[18] Stamler J, Wentworth D, Neaton JD. Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). *Journal of the American Medical Association.* 1986;256(20):2823-2828.

[19] Lipid Research Clinic Program Group. The Lipid Research Clinics Coronary Primary Prevention results. I: Reduction in the incidence of coronary heart disease. *Journal of the American Medical Association.* 1984;251(3):351-364.

[20] Lipid Research Clinics Program Group. The Lipid Research Clinics Coronary Primary Prevention Trial results. II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. *Journal of the American Medical Association.* 1984;251(3):365-374.

In the Framingham Heart Study, over 5,000 men and women who were followed for a period of 14 years showed a direct association between elevated cholesterol levels and the occurrence of ischemic heart disease.[21] A 12 year follow up of 350,977 men in the MRFIT showed a significant and graded association between cholesterol levels and death from CVD.[22,23] The LRCPPT followed 3,806 middle aged men for a period of 7.4 years and established a strong relationship of the causal role of elevated cholesterol on the incidence of CHD.[24,25] In summary, hyperlipidemia is an important risk factor in the development of CHD.

[21] Kannel WB, Castelli WP, Gordon T, et al. Serum cholesterol, lipoproteins, and the risk of coronary heart disease. The Framingham study. *Annals of Internal Medicine.* 1971;74(1):1-12.

[22] Neaton JD, Blackburn H, Jacobs D, et al. Serum cholesterol level and mortality findings for men screened in the Multiple Risk Factor Intervention Trial. Multiple Risk Factor Intervention Trial Research Group. *Archives of Internal Medicine.* 1992;152(7):1490-1500.

[23] Stamler J, Wentworth D, Neaton JD. Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). *Journal of the American Medical Association.* 1986;256(20):2823-2828.

[24] Lipid Research Clinic Program Group. The Lipid Research Clinics Coronary Primary Prevention results. I: Reduction in the incidence of coronary heart disease. *Journal of the American Medical Association.* 1984;251(3):351-364.

[25] Lipid Research Clinics Program Group. The Lipid Research Clinics Coronary Primary Prevention Trial results. II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. *Journal of the American Medical Association.* 1984;251(3):365-374.

Prevalence of High Blood Cholesterol among U.S. Adults

According to the most recent cholesterol management guidelines published in May 2001, cholesterol levels of 200-239 mg/dl are considered borderline-high whereas levels ≥ 240 mg/dl are considered high. An estimated 102.3 million U.S. adults have cholesterol values of 200 mg/dl or higher and approximately 37.7 million adults have levels ≥ 240 mg/dl.[26] Since 1976, blood cholesterol levels among the U.S. adults have decreased substantially. Based on two National Health and Nutrition Examination Surveys (NHANES II and NHANES III), between 1976 and 1991, the percentage of U.S. adults with blood cholesterol levels greater than 240 mg/dl dropped from 26 percent to 20 percent. During the same time period, adults with desirable blood cholesterol levels rose from 44 percent to 49 percent.[27] However, based on the results of the latest NHANES IV conducted between 1999 and 2000, the trend in decreases in total cholesterol concentration appears to have slowed down.[28] A substantial number of U.S. adults are hyperlipidemic. Based on the data from NHANES III, overall 50.7 million (28.2 percent)

[26]Cholesterol statistics. *American Heart Association*. Available at: http://www.americanheart.org/presenter.jhtml?identifier=4506. Accessed February 1, 2005.

[27] Sempos C, Cleeman JI, Carroll M, et al. Prevalence of high blood cholesterol among US adults: an update based on guidelines from the second report of the National Cholesterol Education Program Adult Treatment Panel. *Journal of the American Medical Association.* 1993;269(23):3009-3014.

[28] Ford E, Mokdad A, Giles W, et al. Serum total cholesterol concentrations and awareness, treatment, and control of hypercholesterolemia among US adults: Findings from the National Health and Nutrition Examination Survey 1999 to 2000. *Circulation.* 2003;107(17):2185-2189.

of U.S. adults ≥ 20 years are eligible for treatment based on the Adult Treatment Panel (ATP) II guidelines. As per the ATP II guidelines, 29.5 million (16.4 percent) qualify for dietary therapy alone and 21.2 million (11.8 percent) qualify for drug therapy.[29] Under the new ATP III guidelines, an estimated 36 million Americans will be eligible for drug therapy of which 55 percent are males and 45 percent females. Thirty-two percent of Americans under the age of 45 years, and 28 percent ≥65 years will be eligible for drug therapy for hyperlipidemia.[30]

Primary Causes of Hyperlipidemia

Hyperlipidemia is a lipid abnormality with genetic or familial origins (primary hyperlipidemia). Hyperlipidemia could also be caused by endocrine, hepatic or renal diseases (secondary hyperlipidemia). Primary hyperlipidemia includes familial or polygenic hypercholesterolemia, familial combined hyperlipidemia, familial hypertriglyceridemia, and dysbetalipoproteinemia.[31,32] Different forms of hyperlipidemia

[29] Hoerger TJ, Bala MV, Bray JW, et al. Treatment patterns and distribution of low-density lipoprotein cholesterol levels in treatment-eligible United States adults. *American Journal of Cardiology.* 1998;82(1):61-65.

[30] Fedder DO, Koro CE, L'Italien GJ. New National Cholesterol Education Program III guidelines for primary prevention lipid-lowering drug therapy: projected impact on the size, sex, and age distribution of the treatment-eligible population. *Circulation.* 2002;105(2):152-156.

[31] Grundy SM, Vega GL, Garg A. Use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors in various forms of dyslipidemia. *American Journal of Cardiology.* 1990;66(8):31B-38B.

[32] Farnier M, Davignon J. Current and future treatment of hyperlipidemia: the role of statins. *American Journal of Cardiology.* 1998;82(4B):3J-10J.

can be classified based on the Fredrickson classification of lipoprotein phenotype.[33] Primary hyperlipidemia occurs due to abnormalities in gene encoding of LDL receptors which causes a decrease in the functioning of LDL receptors. This leads to an increase in the LDL concentration since the major pathway of the removal of LDL is via LDL receptors in the liver cells. Increased production of very low-density lipoprotein (VLDL), which is the precursor to LDL, could also result in elevated LDL concentration. In addition to genetic factors, diet can be a significant factor contributing to hyperlipidemia.[34]

Secondary Causes of Hyperlipidemia

Secondary hyperlipidemia occurs as a complication of conditions such as diabetes where poor control of glucose levels could lead to elevated triglyceride levels. Other medical conditions associated with hyperlipidemia include hypothyroidism, liver disease, and Cushing's syndrome.[35] In addition, use of alcohol and drugs such as corticosteroids, thiazide diuretics, estrogen and beta-blockers have also been associated with hyperlipidemia.

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[33] Grundy SM, Vega GL, Garg A. Use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors in various forms of dyslipidemia. *American Journal of Cardiology.* 1990;66(8):31B-38B.

[34] Grundy SM. Cholesterol and coronary heart disease: A new era. *Journal of the American Medical Association.* 1986;256(20):2849-2858.

[35] Chin-Dusting JP, Shaw JA. Lipids and atherosclerosis: clinical management of hypercholesterolaemia. *Expert Opinion on Pharmacotherapy.* 2001;2(3):419-430.

Formation of Atherosclerosis

Hyperlipidemia plays a central role in the development of atherosclerotic plaque that impairs arterial blood flow and could lead to arterial obstruction and myocardial infarction in coronary vessels.[36] The initial development of atherosclerosis occurs due to the deposition of cholesterol in the arteries forming "fatty streaks" on the endothelial surface of the aorta and coronary arteries. The advancement of atherosclerosis is depicted by development of fibrous plaque.[37] Several other processes involved in the development and growth of atherosclerosis including oxidation of LDL, enzyme activity, inflammation, intimal thickening and plaque formation, vascular dysfunction and plaque instability and eventually plaque rupture may result in thrombosis or infarction.[38] Plaque rupture or erosion is responsible for most acute coronary syndromes including myocardial infarction, unstable angina and coronary death.[39]

Oxidized LDL is capable of initiating abnormal arterial wall activation processes that lead to vascular dysfunction.[40] LDL consists of various subspecies that differ in their association with cardiovascular risk. LDL particles that are small and dense have greater

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[36] Farnier M, Davignon J. Current and future treatment of hyperlipidemia: the role of statins. *American Journal of Cardiology.* 1998;82(4B):3J-10J.
[37] Chin-Dusting JP, Shaw JA. Lipids and atherosclerosis: clinical management of hypercholesterolaemia. *Expert Opinion on Pharmacotherapy.* 2001;2(3):419-430.
[38] Selwyn AP, Kinlay S, Ganz P. Atherogenesis and ischemic heart disease. *American Journal of Cardiology.* 1997;80(2):3H-7H.
[39] Libby P, Schoenbeck U, Mach F, et al. Current concepts in cardiovascular pathology: The role of LDL cholesterol in plague rupture and stabilization. *American Journal of Medicine.* 1998;104(2A):14S-18S.
[40] Selwyn AP, Kinlay S, Ganz P. Atherogenesis and ischemic heart disease. *American Journal of Cardiology.* 1997;80(2):3H-7H.

oxidative susceptibility than the larger and buoyant particles.[41] Smaller and denser LDL particles are associated with up to a threefold increase in the risk of myocardial infarction than larger, buoyant LDL particles.[42] The management of hyperlipidemia is crucial in order to prevent CHD, and to do so, it is important to understand the risk factors associated with hyperlipidemia.

Risk Factors for Hyperlipidemia

A number of risk factors have been associated with the occurrence of CHD. Important risk factors include high levels of LDL and triglycerides, low levels of HDL, increasing age, male gender, presence of conditions such as diabetes and hypertension, obesity, smoking status, and family history of CHD. A brief explanation of each of the risk factors is as follows.

LDL, HDL and Triglycerides

High levels of LDL and triglycerides and low levels of HDL are important risk factors for the development of CHD. LDL accounts for most of the association between plasma cholesterol levels and risk of CHD since most of the plasma cholesterol is

[41] Tribble DL, Rizzo M, Chait A, et al. Enhanced oxidative susceptibility and reduced antioxidant content of metabolic precursors of small, dense low-density lipoproteins. *American Journal of Medicine.* 2001;110(2):103-110.
[42] Austin M, Breslow J, Hennekens CH, et al. Low-density lipoprotein subclass patterns and risk of myocardial infarction. *Journal of the American Medical Association.* 1988;260(13):1917-1921.

transported in the LDL. Studies such as the Framingham Heart Study, [43,44] the MRFIT,[45] and the LRCPPT[46,47] have shown a positive association between LDL cholesterol levels and the risk of CHD among men and women initially free of CHD.

Epidemiologic studies such as the Framingham Heart Study have established a negative association between HDL cholesterol levels and the occurrence of CHD.[48,49] Results from the Framingham study showed that HDL cholesterol had an inverse association with the incidence of CHD in both men and women ($p<0.001$). A one percent rise in HDL was associated with a two percent fall in CHD risk.[50] The incidence of CHD was eight times more in individuals with HDL cholesterol below 35 mg/dl than in those

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[43] Castelli WP. Cholesterol and lipids in the risk of coronary heart disease: the Framingham Heart Study. *Canadian Journal of Cardiology.* 1988;4(suppl 1):5A-10A.
[44] Castelli WP, Anderson K, Wilson PW*, et al.* Lipids and risk of coronary heart disease. The Framingham Study. *Annals of Epidemiology.* 1992;2(1-2):23-28.
[45] Stamler J, Wentworth D, Neaton JD. Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). *Journal of the American Medical Association.* 1986;256(20):2823-2828.
[46] Lipid Research Clinic Program Group. The Lipid Research Clinics Coronary Primary Prevention results. I: Reduction in the incidence of coronary heart disease. *Journal of the American Medical Association.* 1984;251(3):351-364.
[47] Lipid Research Clinics Program Group. The Lipid Research Clinics Coronary Primary Prevention Trial results. II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. *Journal of the American Medical Association.* 1984;251(3):365-374.
[48] Gordon T, Castelli WP, Hjortland MC, et al. High density lipoprotein as a protective factor against coronary heart disease: the Framingham Study. *American Journal of Medicine.* 1977;62(5):707-714.
[49] Castelli WP, Garrison RJ, Wilson PW, et al. Incidence of coronary heart disease and lipoprotein cholesterol levels. The Framingham Study. *Journal of the American Medical Association.* 1986;256(20):2835-2838.
[50] Castelli WP. Cholesterol and lipids in the risk of coronary heart disease: the Framingham Heart Study. *Canadian Journal of Cardiology.* 1988;4(suppl 1):5A-10A.

with HDL levels 65 mg/dl or above.[51] A review of trials by Boden, showed that a number of studies such as the CPPT, MRFIT, the Lipid Research Clinics Follow-up Study (LRCF), the Helsinki Heart Study and Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) have also shown a similar inverse relationship between HDL cholesterol and the risk of CHD.[52]

In addition to LDL and HDL, triglycerides also contribute as a risk factor for CHD. In the Framingham Heart Study, triglyceride was an independent risk factor for CHD.[53] Based on a meta-analysis of 17 population-based prospective studies by Hokanson and Austin, elevated triglyceride was associated with a 30 percent and 75 percent increase in cardiovascular risk in men and women, respectively.[54] Triglycerides in conjunction with other risk factors such as high LDL levels and low HDL levels contribute as strong predictors for the development of CHD.[55]

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[51] Gordon T, Castelli WP, Hjortland MC, et al. High density lipoprotein as a protective factor against coronary heart disease: the Framingham Study. *American Journal of Medicine.* 1977;62(5):707-714.

[52] Boden WE. High-density lipoprotein cholesterol as an independent risk factor in cardiovascular disease: Assessing the data from Framingham to the Veterans Affairs High-Density Lipoprotein Intervention Trials. *American Journal of Cardiology.* 2000;86(suppl 12A):19L-22L.

[53] Castelli WP, Anderson K, Wilson PW, et al. Lipids and risk of coronary heart disease. The Framingham Study. *Annals of Epidemiology.* 1992;2(1-2):23-28.

[54] Hokanson JE, Austin MA. Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population-based prospective studies. *Journal of Cardiovascular Research.* 1996;3(2):213-219.

[55] Sprecher DL. Triglyceride as a risk factor for coronary artery disease. *American Journal of Cardiology.* 1998;82(2):49U-56U.

Diabetes

Epidemiologic studies have shown an increased risk of CHD for diabetic patients as compared to non-diabetics. The mortality rates for CHD in diabetic subjects are higher than in non-diabetic subjects. The average annual age-adjusted incidence of CHD per 1000 is 24.8 among diabetic men compared to 14.9 among non-diabetic men. Similarly, the incidence of CHD is 17.8 among diabetic women compared to 6.9 among non-diabetic women.[56] The effect of diabetes on cardiovascular mortality and morbidity is higher for women as compared to men. Low HDL levels in women in the presence of diabetes put women at a higher risk for CHD compared to men.[57]

Hypertension

Hypertension is a major independent risk factor for CHD. Observational studies have demonstrated a strong association between high blood pressure and CHD. This association holds true for both genders and younger as well as older persons.[58,59]

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[56] Kannel WB, McGee DL. Diabetes and glucose tolerance as risk factors for cardiovascular disease: the Framingham study. *Diabetes Care.* 1979;2(2):120-126.

[57] Kannel WB, McGee DL. Diabetes and glucose tolerance as risk factors for cardiovascular disease: the Framingham study. *Diabetes Care.* 1979;2(2):120-126.

[58] Stamler J, Stamler R, Neaton JD. Blood pressure, systolic and diastolic, and cardiovascular risk. US population data. *Archives of Internal Medicine.* 1993;153(5):598-615.

[59] Franklin S, Khan S, Wong ND, et al. Is pulse pressure useful in predicting risk for coronary heart disease? The Framingham Heart Study. *Circulation.* 1999;100(4):354-360.

Obesity

Obesity is an important risk factor for CHD in both men and women.[60,61] Effects of obesity on lipid metabolism are mediated by insulin resistance.[62] Obesity and insulin resistance are both strong predictors of CHD risk.[63] A high prevalence of cardiovascular risk factors such as hypertension, glucose intolerance, hypertriglyceridemia, high total cholesterol and LDL cholesterol and low serum HDL cholesterol among obese patients increases the risk for CHD.[64,65]

Age and Gender

Advancing age and male sex are risk factors for CHD. The risk for older people is higher than in younger people at any given level of LDL cholesterol. Men in their mid-forties (≥ 45 years) and women around the time of menopause (≥ 55 years) are at a

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[60] Denke MA, Sempos CT, Grundy S. Excess body weight: an underrecognized contributor to high blood cholesterol levels in white American men. *Archives of Internal Medicine.* 1993;153(9):1093-1103.

[61] Manson JE, Colditz GA, Stampfer MJ, et al. A prospective study of obesity and risk of coronary heart disease in women. *New England Journal of Medicine.* 1990;322(13):882-889.

[62] Carmena R, Ascaso JF, Real JT. Impact of obesity in primary hyperlipidemias. *Nutrition Metabolism & Cardiovascular Diseases.* 2001;11(5):354-359.

[63] Abbasi F, Brown B, Lamendola C, et al. Relationship between obesity, insulin resistance, and coronary heart disease risk. *Journal of the American College of Cardiology.* 2002;40(5):937-943.

[64] Abbasi F, Brown B, Lamendola C, et al. Relationship between obesity, insulin resistance, and coronary heart disease risk. *Journal of the American College of Cardiology.* 2002;40(5):937-943.

[65] Berchtold P, Berger M, Jorgens V, et al. Cardiovascular risk factors and HDL-cholesterol levels in obesity. *International Journal of Obesity.* 1981;5(1):1-10.

risk for CHD. However, men are at a higher risk for CHD than women at any given age.[66]

Smoking

Cigarette smoking is an important risk factor for CHD and other forms of cardiovascular diseases. In the MRFIT, the numbers of cigarettes smoked per day were significant predictors of death due to CHD in all age groups in combination with risk factors such as high blood pressure and cholesterol.[67] Studies have shown that smoking cessation was related to a reduction in the risk for cardiovascular events.[68,69]

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[66] Wilson PW, D'Agostino RB, Levy D, et al. Prediction of coronary heart disease using risk factor categories. *Circulation.* 1998;97(18):1837-1847.

[67] Neaton JD, Wentworth D. Serum cholesterol, blood pressure, cigarette smoking, and death from coronary heart disease. *Archives of Internal Medicine.* 1992;152(1):56-64.

[68] Willett WC, Green A, Stampfer MJ, et al. Relative and absolute excess risks of coronary heart disease among women who smoke cigarettes. *New England Journal of Medicine.* 1987;317(21):1303-1309.

[69] Wolf PA, D'Agostino RB, Kannel WB, et al. Cigarette smoking as a risk factor for stroke: the Framingham Study. *Journal of the American Medical Association.* 1988;259(7):1025-1029.

Family History of Premature CHD

Several studies have shown that family history of CHD is an independent risk factor for CHD.[70,71,72,73,74] The risk of CHD increases with an increase in the number of first-degree relatives with CHD[75] and the onset of the disease at an early age in the relative.[76] The risk of CHD due to family history is caused by the interaction of genetic and environmental factors.[77,78]

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[70] Shea S, Ottman R, Gabrieli C, et al. Family history as an independent risk factor for coronary artery disease. *Journal of the American College of Cardiology.* 1984;4(4):793-801.

[71] Hopkins PN, Williams RR, Kuida H, et al. Family history as an independent risk factor for incident coronary artery disease in a high-risk cohort in Utah. *American Journal of Cardiology.* 1988;62(10 pt 1):703-707.

[72] Colditz GA, Rimm EB, Giovannucci E, et al. A prospective study of parental history of myocardial infarction and coronary artery disease in men. *American Journal of Cardiology.* 1991;67(11):933-938.

[73] Li R, Bensen JT, Hutchinson RG, et al. Family risk score of coronary heart disease (CHD) as a predictor of CHD: the Atherosclerosis Risk in Communities (ARIC) Study and the NHLBI Family Heart Study. *Genetic Epidemiology.* 2000;18(3):236-250.

[74] Yarnell J, Yu S, Patterson C, et al. Family history, longevity, and risk of coronary heart disease: the PRIME Study. *International Journal of Epidemiology.* 2003;32(1):71-77.

[75] Hopkins PN, Williams RR, Kuida H, et al. Family history as an independent risk factor for incident coronary artery disease in a high-risk cohort in Utah. *American Journal of Cardiology.* 1988;62(10 pt 1):703-707.

[76] Colditz GA, Rimm EB, Giovannucci E, et al. A prospective study of parental history of myocardial infarction and coronary artery disease in men. *American Journal of Cardiology.* 1991;67(11):933-938.

[77] Li R, Bensen JT, Hutchinson RG, et al. Family risk score of coronary heart disease (CHD) as a predictor of CHD: the Atherosclerosis Risk in Communities (ARIC) Study and the NHLBI Family Heart Study. *Genetic Epidemiology.* 2000;18(3):236-250.

[78] Shea S, Ottman R, Gabrieli C, et al. Family history as an independent risk factor for coronary artery disease. *Journal of the American College of Cardiology.* 1984;4(4):793-801.

National Cholesterol Education Program

The National Cholesterol Education Program (NCEP) of the National Institute of Health provides updates and recommendations for cholesterol testing and management. In May 2001, the Third Report on the Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III or ATP III) was released by the NCEP. The ATP III guidelines were preceded by ATP I guidelines released in 1988 and ATP II guidelines released in 1993. The core of ATP III guidelines is based on ATP I and II. The ATP I guidelines outlined a strategy for primary prevention of CHD in individuals with high or borderline high LDL cholesterol and multiple risk factors. ATP II guidelines focused both on the primary and secondary prevention of CHD. Based on the results from recent clinical trials, ATP III calls for a more intensive LDL lowering and focuses on primary prevention in persons with multiple risk factors.[79] Both ATP II and ATP III guidelines will be discussed because patients in this study overlapped the time periods between the two guidelines. The main highlights of guidelines are described below.

[79] Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *Journal of the American Medical Association.* 2001;285(19):2486-2497.

Adult Treatment Panel II

As per ATP II guidelines, dietary therapy is recommended as the first line of treatment for hyperlipidemia. Drug therapy is reserved for patients at a high risk for CHD. Patients are classified into three risk factor categories ranging from very high to low based on the presence of risk factors and prior CHD event. ATP II continues to identify elevated LDL as the primary target of cholesterol-lowering therapy. ATP II classifies blood cholesterol into three categories which are desirable, borderline and high blood cholesterol.[80]

Table 1.1: Initial Classification of Blood Cholesterol Based on Total Cholesterol Based on ATP II Guidelines

Cholesterol Level	**Initial Classification**
<200 mg/dl	Desirable blood cholesterol
200-239 mg/dl	Borderline-high blood cholesterol
≥240 mg/dl	High blood cholesterol

Adapted from*: JAMA* 1993;269(23):3015-3023

[80] Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults. Summary of the Second Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *Journal of the American Medical Association.* 1993;269(23):3015-3023.

Factors (other than elevated LDL) that increase the risk of CHD as per ATP II include:[81]

- Age (men > 45 years; women > 55 years)
- Family history of premature CHD (definite myocardial infarction or sudden death before 55 years of age in father or other male first-degree relative, or before 65 years of age in mother or other female first-degree relative)
- Current cigarette smoking
- Hypertension (≥ 140/90 mmHg, or on antihypertensive medication)
- Low HDL cholesterol (< 35 mg/dl)

Table 1.2: LDL Cholesterol Goals and Cutpoints for Treatment Decisions Based on ATP II Guidelines

Risk Category	LDL Goal (mg/dl)	LDL Level at Which to Initiate Dietary Therapy (mg/dl)	LDL Level at Which to Consider Drug Therapy (mg/dl)
Without CHD and < 2 risk factors	< 160	≥ 160	≥ 190
Without CHD and ≥ 2 risk factors	< 130	≥ 130	≥ 160
With CHD	≤ 100	>100	≥ 130

Adapted from: *JAMA.* 1993;269(23):3015-3023.

[81] Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults. Summary of the Second Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *Journal of the American Medical Association.* 1993;269(23):3015-3023.

ATP II guidelines recommend dietary therapy in patients with LDL levels of 160 mg/dl or greater and fewer than two other CHD risk factors or in patients with LDL levels above 130 mg/dl and presence of two or more other CHD risk factors. In patients with CHD, dietary therapy should be initiated if LDL levels are greater than 100 mg/dl. If the LDL levels do not reach the desired levels with dietary therapy, drug therapy may be considered.

For patients with low HDL levels, the panel recommends physical activity, smoking cessation and, in the case of obese patients, weight loss as first line of treatment. Drug therapy should be reserved for individuals with high LDL levels in addition to low HDL levels. For younger men and premenopausal women, drug therapy should only be considered at very high LDL levels (220 mg/dl) or in the presence of multiple other risk factors such as diabetes or family history of premature CHD. In postmenopausal women with high LDL cholesterol levels, the panel recommends considering the use of estrogen replacement therapy. However, the ATP III guidelines are against this recommendation.

Drug therapy should be considered in patients with LDL levels of 190 mg/dl or greater and fewer than two other CHD risk factors or 160 mg/dl or greater in patients with two or more CHD risk factors. In secondary prevention patients, (i.e. patients with prior CHD and/or atherosclerotic disease), drug therapy should be started when LDL levels are 130 mg/dl or higher.

After initiating lipid-lowering drug therapy, LDL levels should be measured at four to six weeks and then at three months. If patients achieve the LDL goals then they should be seen every four months to monitor their response to the drug as well as potential side effects. If the initial drug therapy is inadequate, the patient should be switched to another drug or combination therapy should be used. The guidelines emphasize the "vigorous efforts at dietary therapy" prior to initiation of drug therapy. In May 2001, the NCEP introduced a new set of guidelines (ATP III) for the management of high cholesterol. The important features of the new guidelines are discussed below.

New Features of ATP III

The new features of ATP III are summarized as follows. The following section has been adapted from the executive summary of the guidelines in the *Journal of the American Medical Association*.[82]

Focus on Multiple Risk Factors

- Raises persons with diabetes without CHD, most of whom have multiple risk factors, to the risk level of CHD risk equivalent

[82] Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *Journal of the American Medical Association.* 2001;285(19):2486-2497.

- Uses Framingham projections of 10-year absolute CHD risk (i.e. the percent probability of having a CHD event in 10 years) to identify certain patients with multiple (2+) risk factors for more intensive treatment
- Identifies persons with multiple metabolic risk factors (metabolic syndrome) as candidates for intensified therapeutic lifestyle changes

Modifications of Lipid and Lipoproteins Classification

- Identifies LDL cholesterol < 100 mg/dl as optimal.
- Raises categorical low HDL cholesterol from < 35 mg/dl to < 40 mg/dl because the latter is a better measure of a depressed HDL.
- Lowers the triglyceride classification cutpoints to give more attention to moderate elevations.

Support for implementation

- Recommends a complete lipoprotein profile (total, LDL and HDL cholesterol and triglycerides) as the preferred initial test, rather than screening for total cholesterol and HDL alone.
- Encourages use of plant stanols/sterols and viscous (soluble) fiber as therapeutic dietary options to enhance lowering of LDL cholesterol.
- Presents strategies for promoting adherence to therapeutic lifestyle changes and drug therapies.
- Recommends treatment beyond LDL lowering for persons with triglycerides $\geq$ 200 mg/dl.

The following features are shared by ATP II and ATP III guidelines:

- Continued identification of LDL cholesterol lowering as the primary goal of therapy.
- Consideration of high LDL cholesterol (≥160 mg/dl) as a potential target for LDL-lowering drug therapy.
- Emphasis on intensive LDL-lowering therapy in persons with established CHD.
- Identification of three categories of risk for different LDL goals and different intensities of LDL-lowering therapy.
- Identification of three subpopulations, besides middle-aged men, for detection of high LDL cholesterol and other lipid risk factors for intervention.
- Emphasis on weight loss and physical activity to enhance risk reduction in persons with elevated LDL cholesterol.

Based on the above risk factors, ATP III identifies three categories of risk that modify the goals of LDL-lowering therapy.

1. The category with the highest risk consists of CHD and CHD risk equivalent. Individuals with risk level of CHD risk equivalent and without established CHD will have an absolute, 10-year risk for developing major coronary events equal to that of a person with CHD, i.e. > 20 percent per 10 years (i.e., more than 20 in 100 such individuals will develop CHD or have CHD events within 10 years). CHD risk equivalent consists of :

- Other clinical forms of atherosclerotic disease (including peripheral arterial disease, abdominal aortic aneurysm, and symptomatic carotid artery disease).
- Diabetes (diabetes counts as a CHD risk factor as it confers a high risk of new CHD within 10 years, partly due to its association with other multiple risk factors).
- Multiple risk factors that confer a 10-year risk for CHD > 20 percent.

The LDL cholesterol goal for individuals with CHD or CHD risk equivalents is the lowest (< 100 mg/dl).

2. The second category consists of individuals with multiple (two or more) risk factors, in whom 10-year risk for CHD is $\leq$ 20 percent. The LDL goal for individuals in this category is < 130 mg/dl.
3. The third category consists of individuals with 0-1 risk factor. Most persons in this category have a 10-year risk for CHD of less than 10 percent. The LDL cholesterol goal is < 160 mg/dl.

The ATP III guidelines cholesterol treatment goals are summarized in the Table 1.3.

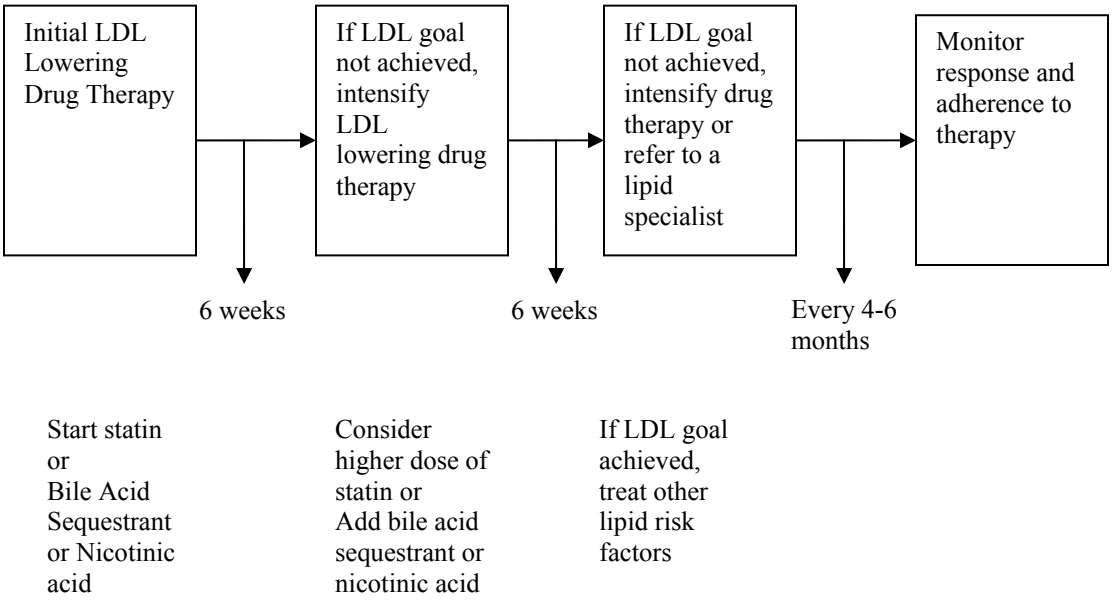
Table 1.3: LDL Cholesterol Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug therapy in Different Risk Categories Based on ATP III

Risk Category	**LDL Goal (mg/dl)**	**LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dl)**	**LDL Level at Which to Consider Drug Therapy (mg/dl)**
CHD or CHD equivalents (10-year risk > 20%)	< 100	≥ 100	≥ 130 (100-129: drug optional)
2 + Risk Factors (10-year risk ≤ 20%)	< 130	≥ 130	10-year risk 10-20%: ≥ 130 10-year risk < 10%: ≥ 160
0-1 Risk Factors	< 160	≥ 160	≥ 190 (160-189: drug optional)

Adapted from: JAMA 2001; 285(19):2486-97

The ATP III guidelines present the following algorithm for the use of drug therapy for primary prevention of CHD.

Figure 1.1: Progression of Drug Therapy in Primary Prevention as per ATP III Guidelines



Adapted from JAMA 2001; 285(19):2486-97

Management of Hyperlipidemia

The two main approaches to the management of hyperlipidemia are lifestyle modification such as dietary intervention and/or lipid-lowering drugs.

Dietary Management of Hyperlipidemia

Dietary management is the initial step of therapeutic lifestyle changes for the management of hyperlipidemia. In most cases, diet management should be initiated prior to drug therapy. ATP III recommends the reduced intake of saturated fats and cholesterol and increased intake of agents such as plant stanols/sterols and increased soluble fiber for the lowering of LDL levels.[83] Diet can also help control CHD risk factors such as obesity, hypertension and diabetes. In addition to diet therapy, weight reduction and increased physical activity are also recommended as a part of therapeutic lifestyle changes for the management of hyperlipidemia.[84]

[83] Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *Journal of the American Medical Association.* 2001;285(19):2486-2497.

[84] Kreisberg RA, Oberman A. Medical management of hyperlipidemia/dyslipidemia. *Journal of Clinical Endocrinology & Metabolism.* 2003;88(6):2445-2461.

Pharmacological Management of Hyperlipidemia

A portion of patients with a high-risk for CHD will require lipid-lowering drugs in addition to dietary therapy. The major drugs used in the treatment of hyperlipidemia include fibrates, bile acid sequestrants, nicotinic acid derivatives, estrogen replacement therapy and statins. The following section provides an overview of each of drugs used in the treatment of hyperlipidemia.

Fibrates

Fibric acid derivatives (fibrates) are used in adjunct with dietary modification in adults with primary hyperlipidemia or mixed dyslipidemias. Currently, in the U.S. there are two fibrates available: gemfibrozil and fenofibrate. The main indication for fibrates is reduction of triglycerides. The LDL lowering effects of fenofibrates range between 15 to 20 percent when triglycerides are not elevated. However, in persons with hypertriglyceridemia, fibrates are known to increase LDL-cholesterol levels.[85] Fibrates decrease triglyceride levels by 25-50 percent and increase the HDL cholesterol levels by 10-35 percent.[86] Fenofibrates decreased the triglycerides and VLDL-cholesterol levels by 38 percent, total cholesterol by 17 percent and LDL by 20 percent, and increased HDL

[85] Knopp RH, Brown WV, Dujovne CA, et al. Effects of finofibrate on plasma lipoproteins in hypercholesterolemia and combined hyperlipidemia. *American Journal of Medicine.* 1987;83(5):50-59.
[86] Leaf DA, Connor WE, Illingworth DR, et al. The hypolipidemic effects of gemfibrozil in type V hyperlipidemia: a doube-blind, crossover study. *Journal of the American Medical Association.* 1989;262(22):3154-3160.

by 11 percent.[87] Fibrates mainly act by increasing the lipoprotein lipase activity which increases fatty acid oxidation thereby reducing the formation of triglycerides.[88] Fibrates also cause reduction in the size of the LDL particles which result in an increased resistance of LDL to oxidation.[89]

Gemfibrozil therapy reduces in the risk of cardiovascular events mainly due to an increase in HDL levels and a decrease in triglycerides among secondary prevention patients. In a double-blind trial of 2531 men with CHD, a 24 percent reduction in death due to CHD, non-fatal myocardial infarction and stroke was observed in the gemfibrozil group compared to the placebo group.[90] In the Helsinki Heart Study, gemfibrozil treatment was associated with a 37 percent reduction in fatal and non-fatal myocardial infarctions.[91] Fibrates are generally well-tolerated; however, gastrointestinal complications are common side effects of this drug class. They appear to increase the

[87] Knopp RH, Brown WV, Dujovne CA, et al. Effects of finofibrate on plasma lipoproteins in hypercholesterolemia and combined hyperlipidemia. *American Journal of Medicine.* 1987;83(5):50-59.
[88] Schwandt P. Fibrates and triglyceride metabolism. *European Journal of Clinical Pharmacology.* 1991;40 (suppl 1):S41-S43.
[89] Staels B, Dallongeville J, Auwerz J, et al. Mechanism of action of fibrates on lipid and lipoprotein metabolism. *Circulation.* 1998;98(19):2088-2093.
[90] Rubins HB, Robins SJ, Collins D, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. *New England Journal of Medicine.* 1999;341(6):410-418.
[91] Frick M, Elo O, Haapa K, et al. Helsinki Heart Study: Primary-prevention trial with Gemfibrozil in middle-aged men with dyslipidemia. *Journal of the American Medical Association.* 1987;317(20):1237-1245.

lithogenecity of bile acids and thus, increase the likelihood of the formation of cholesterol gallstones.[92]

Bile acid resins

Bile acid resins include cholestyramine, colestipol, and colesevelam. The main action of bile acids resins is to lower LDL cholesterol. They act by binding bile acids in the intestine thereby promoting excretion of bile acids in the feces. Bile acids are formed in the liver from the degradation of cholesterol. Due to the depletion of bile acids, their hepatic synthesis is increased. An increased amount of cholesterol is transported to the liver for the production of bile acids which results in a decrease in intrahepatic cholesterol.[93] Bile acid sequestrants reduce LDL cholesterol by 20 percent and triglycerides levels by 5-20 percent. In the Lipid Research Clinics Coronary Primary Prevention Trial, treatment with cholestyramine reduced the risk of CHD.[94,95]

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[92] Palmer RH. Effects of fibric acid derivatives on biliary lipid composition. *American Journal of Medicine.* 1987;83(suppl 5B):37-43.
[93] Shepherd J. Mechanism of action of bile acid sequestrants and other lipid-lowering drugs. *Cardiology.* 1989;76(suppl 1):65-74.
[94] Lipid Research Clinic Program Group. The Lipid Research Clinics Coronary Primary Prevention results. I: Reduction in the incidence of coronary heart disease. *Journal of the American Medical Association.* 1984;251(3):351-364.
[95] Lipid Research Clinics Program Group. The Lipid Research Clinics Coronary Primary Prevention Trial results. II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. *Journal of the American Medical Association.* 1984;251(3):365-374.

Bile acids are often poorly tolerated due to side effects such as bloating, abdominal discomfort, nausea and constipation.[96] Moreover, when taken concurrently, they inhibit the absorption of drugs such as digitalis glycosides, thiazides diuretics, beta-blockers, warfarin, and exogenous thyroid hormones.[97] Another disadvantage of bile acid sequestrants includes an increase in triglyceride concentrations in some patients. Addition of statins to the bile acid therapy can inhibit this activity.[98] Colesevelam is a newer bile acid sequestrant currently launched in the U.S. which has fewer side effects than the other bile acids.[99]

Nicotinic Acid

Nicotinic acid or niacin inhibits the transport of free fatty acids from peripheral tissues to the liver. This leads to the reduction in the hepatic synthesis of triglycerides and the hepatic secretion of very low density lipoprotein. It may also limit the conversion of VLDL to LDL. Nicotinic acid can increase the HDL levels by up to 30 percent.[100]

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[96] Chin-Dusting JP, Shaw JA. Lipids and atherosclerosis: clinical management of hypercholesterolaemia. *Expert Opinion on Pharmacotherapy.* 2001;2(3):419-430.
[97] Cziraky M. Clinical positioning of HMG-CoA reductase inhibitors in lipid management protocols. *Pharmacoeconomics.* 1998;14(suppl 3):29-38.
[98] Shepherd J. Mechanism of action of bile acid sequestrants and other lipid-lowering drugs. *Cardiology.* 1989;76(suppl 1):65-74.
[99] Steinmetz K. Colesevelam hydrochloride. *American Journal of Health System Pharmacy.* 2002;59(10):932-939.
[100] Knopp RH. Drug treatment of lipid disorders. *New England Journal of Medicine.* 1999;341(7):498-411.

Studies have shown decreased risk in total mortality[101] and morbidity from CHD[102] in patients treated with niacin.

The use of niacin in combination with statin therapy has been cautioned due to case reports of the occurrence of myopathy.[103] The major side-effect of nicotinic acid is flushing of the skin. Other side-effects are conjunctivitis, nasal stuffiness, diarrhea and itching.[104] A new extended-release preparation of niacin (Niaspan®) has shown to have fewer side effects of vasodilatory skin reaction than the usual preparations.[105]

Estrogen Replacement Therapy

The use of estrogen replacement therapy (ERT) to reduce the risk of CHD in postmenopausal women have been subject to mixed results.[106] Some observational and randomized trials have shown beneficial effects of ERT on CHD. O'Keefe et al., showed that ERT improved the overall survival of postmenopausal women following the first episode of percutaneous transluminal coronary angioplasty (PTCA) compared with

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[101] Canner P, Berge K, Wenger N, et al. Fifteen year mortality in Coronary Drug Project patients: long-term benefit with niacin. *Journal of the American College of Cardiology.* 1986;8(6):1245-1255.

[102] Coronary Drug Project Research Group. Clofibrate and niacin in coronary heart disease. *Journal of the American Medical Association.* 1975;231(4):360-381.

[103] Reaven P, Witztum J. Lovastatin, nicotinic acid and rhabdomylosis. *Annals of Internal Medicine.* 1988;109(7):597-598.

[104] Knopp RH. Drug treatment of lipid disorders. *New England Journal of Medicine.* 1999;341(7):498-411.

[105] Guyton JR, Goldberg AC, Kreisberg RA, et al. Effectiveness of once-nightly dosing of extended-release niacin alone and in combination for hypercholesterolemia. *American Journal of Cardiology.* 1998;82(6):737-743.

[106] Khan S, Malhotra S. Effect of hormone replacement therapy on cardiovascular disease: current opinion. *Expert Opinion on Pharmacotherapy.* 2003;4(5):667-674.

placebo (93 percent vs. 73 percent).[107] In the Nurses' Health Study, 2489 women with a history of CHD showed an increase in relative risk for major CHD to 1.25 (95% Confidence Interval (CI): 0.78 - 2.00) with use of ERT. However, after long-term hormone use, the rate of CHD events was lower in patients on hormone therapy compared with those who had never used hormone therapy (RR=0.38, 95% CI: 0.22-0.66).[108] Based on two meta-analyses conducted by Barrett-Connor and Grady et al. hormone therapy lowered the incidence of cardiovascular diseases among users by 35 percent.[109,110]

Some studies such as the Women's Health Initiative Trial showed an increased risk of stroke by 37 percent in women who were part of the estrogen plus progestin group compared to those who had never been on hormone therapy. The study concluded that estrogen plus progestin increased the risk of stroke in postmenopausal women who were in general in good health.[111] Recently published results recommend against the

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[107] O'Keefe J, Kim SC, Hall R, et al. Estrogen replacement therapy after coronary angioplasty in women. *Journal of the American College of Cardiology.* 1997;29(1):1-5.

[108] Grodstein F, Stampfer MJ, Manson JE, et al. Postmenopausal estrogen and progestin use and the risk of cardiovascular disease. *New England Journal of Medicine.* 1996;335(7):453-461.

[109] Barrett-Connor E. Postmenopausal estrogen and heart disease. *Atherosclerosis.* 1995;118(suppl):S7-10.

[110] Grady D, Rubin S, Petitti D, et al. Hormone therapy to prevent disease and prolong life in post-menopausal women. *Annals of Internal Medicine.* 1992;117(12):1016-1037.

[111] Smoller-Wassertheil S, Hendrix S, Limacher M, et al. Effect of estrogen plus progestin on stroke in postmenopausal women: The Women's Health Initiative: A randomized trial. *Journal of the American Medical Association.* 2003;289(20):2673-2684.

prescribing of hormone replacement therapy for protection against cardiovascular disease.[112]

Similarly, the Heart and Estrogen/Progesterone Replacement Study (HERS) concluded that ERT did not lower the risk of CHD among postmenopausal women.[113] Furthermore, an additional follow up of the women in the HERS study for 6.8 years showed no reduction in the risk of cardiovascular disease and advised against the use of hormone therapy to reduce the risk of CHD events.[114] Hormone therapy also failed to show a significant effect on the progression of atherosclerosis.[115,116] The ATP III does not favor the use of HRT in the prevention of CHD in postmenopausal women.[117]

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[112] Manson J, Hsia J, Johnson K, et al. Estrogen plus progestin and the risk of coronary heart disease. *New England Journal of Medicine.* 2003;349(6):523-534.

[113] Hulley S. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *Journal of the American Medical Association.* 1998;280(7):605-613.

[114] Grady D, Herrington D, Bittner V, et al. Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and estrogen/progestin replacement study follow-up (HERS-II). *Journal of the American Medical Association.* 2002;288(1):49-57.

[115] Hodis HN, Mack WJ, Azen SP, et al. Hormone therapy and the progression of coronary-artery atherosclerosis in postmenopausal women. *New England Journal of Medicine.* 2003;349(6):535-545.

[116] Herrington D, Reboussin D, Brosnihan K, et al. Effects of estrogen replacement on the progression of coronary-artery atherosclerosis. *New England Journal of Medicine.* 2000;343(8):522-529.

[117] Grundy SM, Becker DM, Clark L, et al. Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *Journal of the American Medical Association.* 2001;285(19):2486-2497.

Statins

Statins, also known as 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors, are the most commonly prescribed medications for hyperlipidemia and are recommended as first line therapy under ATP III guidelines. Currently there are six statins available in the U.S. market. The earlier statins, lovastatin (Mevacor® by Merck marketed in 1987) and pravastatin (Pravachol® by Bristol-Myers Squibb, marketed in 1991), were isolated from fungal cultures. Simvastatin (Zocor® by Merck marketed in 1992) is a semi-synthetic derivative whereas fluvastatin (Lescol® by Novartis, marketed in 1992) was the first entirely synthetic compound. A new generation of synthetic statins include atorvastatin (Lipitor® by Parke-Davis, marketed in 1996) and the most recent rosuvastatin (Crestor® by AstraZeneca, marketed in 2003). Cerivastatin (Baycol® by Bayer, marketed in 1998), a synthetic statin, was withdrawn from the market in 2001 due to the occurrence of fatal rhabdomylosis.

According to data compiled by IMS Health, in 2003, cholesterol and triglyceride reducers, of which statins make up a vast majority, comprised the world's second largest therapy class with sales of $16 billion.[118] The two top selling statins, Lipitor® and Zocor®, were the top selling drugs in 2003, accounting for $12.5 billion in sales.[119]

[118] Are statins wonder drugs. IMS Health. URL: http://www.ims-global.com/insight/news_story/0104/news_story_010404.htm Accessed on 10/1/2003.
[119] Barrett A. A bare-knuckle battle over cholesterol drugs. *Business Week Online*; 2003.

Statins have proven to be effective in the treatment of various forms of hyperlipidemia.[120] Statins act by inhibiting the synthesis of cholesterol. They do so by inhibiting the HMG-CoA reductase enzyme that acts as a catalyst in the synthesis of cholesterol.[121] The reduction in the hepatocyte cholesterol concentration leads to an increased number of LDL receptors which increases the clearance of LDL from the circulation.[122] In addition to this, statins reduce the production and secretion of lipoproteins.[123] Depending upon the statin and the dose administered, LDL reduction ranges from 18-55 percent. The increase in HDL levels range from 5-10 percent, whereas the decrease in triglycerides ranges from 7-30 percent.[124]

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[120] Grundy SM, Vega GL, Garg A. Use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors in various forms of dyslipidemia. *American Journal of Cardiology.* 1990;66(8):31B-38B.

[121] Shepherd J. The statin era: in search of the ideal lipid regulating agent. *Heart.* 2001;85(3):259-264.

[122] Grundy S. HMG-CoA reductase inhibitors for treatment of hypercholesterolemia. *New England Journal of Medicine.* 1988;319(1):24-33.

[123] Slater E, MacDonald J. Mechanism of action and biological profile of HMG-CoA reductase inhibitors: a new therapeutic alternative. *Drugs.* 1988;36(suppl 3):72-82.

[124] Jones P, Kafonek S, Laurora I, et al. Comparative dose efficacy study of atorvastatin versus simvastatin, pravastatin, lovastatin, and fluvastatin in patients with hypercholesterolemia (the CURVES study). *American Journal of Cardiology.* 1998;81(5):582-587.

Comparison of statins

Statins differ in their ability to lower the LDL levels. Knopp et al. compared the properties of six statins available in 1999 in the U.S. (Table 1.4).[125] In addition, information on rosuvastatin obtained from the package insert has been inserted in Table 1.4. For all six statins, the dose-response relationship was curvilinear. Doubling the dose above the minimal effective dose decreased the LDL levels by an additional six percent. The maximum reduction in LDL concentration ranged from 24 to 60 percent.[126] The comparison of the effect of different statins on the lipid and lipoprotein levels is shown in Table 1.5.[127]

Rosuvastatin is the newest statin launched in the later half of 2003. Rosuvastatin has been shown to reduce the LDL cholesterol levels by up to 63 percent. Data from five randomized, double-blind, parallel-group, comparator-controlled trials were pooled to compare the efficacy of rosuvastatin 5 mg and 10 mg with atorvastatin 10 mg, simvastatin 20 mg and pravastatin 20 mg. Both doses of rosuvastatin were significantly associated with greater reduction in LDL levels than atorvastatin ($p<0.001$), simvastatin ($p<0.001$) and pravastatin ($p<0.001$). Rosuvastatin showed consistent efficacy across all

[125] Knopp RH. Drug treatment of lipid disorders. *New England Journal of Medicine.* 1999;341(7):498-411.
[126] Knopp RH. Drug treatment of lipid disorders. *New England Journal of Medicine.* 1999;341(7):498-411.
[127] Maron DJ, Fazio S, Linton MF. Current Perspectives on Statins. *Circulation.* 2000;101(2):207-213.

patient subgroups.[128,129] Rosuvastatin was more effective than atorvastatin, pravastatin and simvastatin in meeting the NCEP ATP III goals.[130]

[128] Blasetto J, Stein EA, Brown WV, et al. Efficacy of Rosuvastatin compared with other statins at selected starting doses in hypercholesterolemic patients and in special population groups. *American Journal of Cardiology.* 2003;91(suppl):3C-10C.

[129] Jones P, Davidson MH, Stein EA, et al. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR Trial). *American Journal of Cardiology.* 2003;92(2):152-160.

[130] Shepherd J, Hunninghake D, Barter P, et al. Guidelines for lowering lipids to reduce coronary artery disease risk: A comparison of Rosuvastatin with Atorvastatin, Pravastatin, and Simvastatin for achieving lipid-lowering goals. *American Journal of Cardiology.* 2003;91(suppl):11C-19C.

Table 1.4 Maximal Dose, Cholesterol and Triglyceride Lowering and Pharmacokinetic Properties of Statins

Properties	Lovastatin (Mevacor®)	Pravastatin (Pravachol®)	Simvastatin (Zocor®)	Atorvastatin (Lipitor®)	Fluvastatin[b] (Lescol®)	Cerivastatin (Baycol®)	Rosuvastatin[c] (Crestor®)
Maximal dose (mg/day)	80	40	80	80	40	0.3	40
Maximal serum LDL-cholesterol reduction produced (%)	40%	34%	47%	60%	24%	28%	63%
Serum LDL-cholesterol reduction produced (%)[a]	34%	34%	41%	50%	24%	28%	63%
Serum TG reduction produced (%)[a]	16%	24%	18%	29%	10%	28%	28%
Serum HDL-cholesterol increase (%)[a]	8.6%	12%	12%	6%	8%	10%	10%
Plasma half-life (hr)	8.6	12	12	6	8	10	19
Effect of food on absorption of drug	Increased	Decreased	None	None	Negligible	None	None
Optimal administration time	With meals	Bedtime	Evening	Evening	Bedtime	Evening	Anytime
Penetration of CNS	Yes	No	Yes	No	No	Yes	No
Renal excretion of absorbed dose (%)	10%	20%	13%	2%	<6%	33%	28%
Mechanism of hepatic metabolism	C-P450 3A4	Sulfation	C-P4503A4	C-P4503A4	C-P4502C9	CYP-4503A4 CYP-450 2C8	CYP-450 2C9

[a] The effect was elicited by a daily dose of 40 mg of lovastatin, pravastatin, simvastatin, atorvastatin, fluvastatin and rosuvastatin in patients with hypercholesterolemia

[b] In October 2000, fluvastatin 80 mg/day was approved and the serum LDL cholesterol reduction associated with it is 34-36%

[c] Information obtained from Rosuvastatin package insert, AstraZeneca Pharmaceuticals LP, Wilmington, DE. 2003

Adapted from: Knopp RH: NEJM 1999;341(7):498-511

Table 1.5: Comparative Efficacy of The Six Statins on Lipids and Lipoprotein in Patients Without Hypertriglyceridemia

Statin Drug and Dose (mg)						Change in Lipid and Lipoprotein Levels			
Atorvastatin	Simvastatin	Lovastatin	Pravastatin	Fluvastatin	Cerivastatin	Total	LDL	HDL	Triglycerides
---	10 mg	20 mg	20 mg	40 mg	0.2 mg	-22%	-27%	+4-8%	-10-15%
10 mg	20 mg	40 mg	40 mg	80 mg	0.4 mg	-27%	-34%	+4-8%	-10-20%
20 mg	40 mg	80 mg	---	---	---	-32%	-41%	+4-8%	-15-25%
40 mg	80 mg	---	---	---	---	-37%	-48%	+4-8%	-20-30%
80 mg	---	---	---	---	---	-42%	-55%	+4-8%	-25-35%

Adapted: Maron et al. *Circulation* 2000;101(2):207-213.

Combination therapy

Combination therapy of statins with other lipid-lowering drugs may be necessary in lowering LDL levels in order to attain the NCEP goals. Bile acids, niacin or fibrates are used in combination with statins to achieve the NCEP goals. However, combination therapy needs to be closely monitored due to increased risk of rhabdomylosis.[131]

Taher et al. conducted a retrospective chart review of 136 patients on combination therapy and found that eight percent of the patients had to discontinue the treatment due to the occurrence of muscle pain. However, overall the statin-fibrate and statin-niacin combination was safe and well tolerated by most patients.[132] The decision to combine statin therapy with a fibrate or niacin is often influenced by baseline levels of triglycerides and HDL cholesterol. In patients with low-HDL, niacin might be a good choice as an add-on therapy whereas when triglycerides are elevated, fibrates are effective.[133] Newer agents such as ezetimibe (Zetia®, by Schering-Plough Corporation, marketed in 2002) can be used in combination with statins. Ezetimibe is a part of a new class of lipid-lowering drugs that are called cholesterol absorption inhibitors. When added to statin therapy, ezetimibe reduced LDL cholesterol by an additional 14 percent

[131] Brown AS. Use of combination therapy for dyslipidemia: a lipid clinic approach. *American Journal of Cardiology*. 2002;90(2):44-49.
[132] Taher TH, Dzavik V, Reteff EM*, et al.* Tolerability of statin-fibrate and statin-niacin combination therapy in dyslipidemic patients at high risk for cardiovascular events. *American Journal of Cardiology*. 2002;89(4):390-394.
[133] Rosenson RS. The rationale for combination therapy. *American Journal of Cardiology*. 2002;90(2):2-7.

when used with simvastatin and an additional 12 percent with atorvastatin. Ezetimibe appears to be well tolerated with few side effects.[134]

Safety of Statins

Statins are generally well tolerated by most patients, however, the use of statins has been associated with myopathy, which is defined as "muscle pain or weakness associated with creatine kinase levels higher than 10 times the upper normal limit."[135] Myopathy occurs more frequently in statins in conjunction with drugs that inhibit the cytochrome P450 pathway and in patients with impaired drug metabolism.[136] The American College of Cardiology/American Heart Association clinical advisory on the use and safety of statins put forth four syndromes associated with statin use including statin myopathy, myalgia, myositis and rhabdomylosis.[137] Statin-associated myopathy is dose related. For example, the incidence rate of myopathy increases four to five-fold by increasing the dose of simvastatin or atorvastatin from 40 mg to 80 mg.[138] Statin

[134] Mckenney J. Combination therapy for elevated low-density lipoprotein cholesterol: the key to coronary artery disease risk reduction. *American Journal of Cardiology.* 2002;90(suppl):8K-20K.
[135] Maron DJ, Fazio S, Linton MF. Current Perspectives on Statins. *Circulation.* 2000;101(2):207-213.
[136] Davidson MH. Does differing metabolism by cytochrome P450 have clinical importance. *Current Atherosclerosis Reports.* 2000;2(1):14-19.
[137] Pasternak RC, Smith S, Bairey-Merz CN, et al. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *Journal of the American College of Cardiology.* 2002;40(3):567-572.
[138] Davidson MH. Combination therapy for dyslipidemia: safety and regulatory considerations. *American Journal of Cardiology.* 2002;90(2):50-60.

associated rhabdomylosis is rare with an incidence of 0.15 deaths per one million prescriptions (of cerivastatin).[139] Based on an update of the FDA reports on statin-associated rhabdomylosis, between the periods of January 1, 1990 through March 31, 2002, a total of 3339 cases were identified. Cerivastatin was most often linked with the occurrence of rhabdomylosis (57%) followed by simvastatin (18%) and atorvastatin (12%).[140] Due to increased report of deaths related to rhabdomylosis, cerivastatin was eventually withdrawn from the market in 2001.[141]

The combination of statins with fibrates appears to be an attractive option due to increased LDL lowering compared with monotherapy; however, several case reports have been published regarding the occurrence of rhabdomylosis with statin-fibrates combination. As per the reports, the risk levels for statin-gemfibrozil combination therapy are much higher than those of a statin and fenofibrate.[142] The incidence rates for myopathy are lower with the statin-niacin combination than with statin-gemfibrozil combination.[143] However, the incidence of rhabdomylosis appears to be relatively low in

[139] Staffa J, Chang J, Green L. Cerivastatin and reports of fatal rhabdomylosis. *New England Journal of Medicine.* 2002;346(7):539-540.
[140] Thompson P, Clarkson P, Karas R. Statin-associated myopathy. *Journal of the American Medical Association.* 2003;289(13):1681-1690.
[141] Thompson CA. Cerivastatin withdrawn from market. *American Journal of Health System Pharmacy.* 1685;58(18):15.
[142] Davidson MH. Combination therapy for dyslipidemia: safety and regulatory considerations. *American Journal of Cardiology.* 2002;90(2):50-60.
[143] Omar MA, Wilson J, Cox TS. Rhabdomylosis and HMG-CoA reductase inhibitors. *Annals of Pharmacotherapy.* 2001;35(9):1096-1107.

patients who are monitored and when the statin doses are low.[144] The risk of rhabdomylosis increases with the concomitant use of statins and cyclosporine in heart transplant patients.[145] Other adverse effects of statins include dyspepsia, gastrointestinal disturbances, central nervous system disturbances and sleep disorders and headaches.[146,147] In summary, patients on high doses of statins and those on combination therapy need to be monitored for rhabdomylosis and other potential side-effects.

[144] Pogson GW, Kindred LH, Carper BG. Rhabdomyolysis and renal failure associated with cerivastatin-gemfibrozil combination therapy. *American Journal of Cardiology.* 1999;83(7):1146.
[145] Rodriguez J. Rhabdomylosis in heart transplant patients on HMG-CoA reductase inhibitors and cyclosporine. *Transplantation Proceedings.* 1999;31(6):2522-2523.
[146] SteinerA, Weisser B, Vetter WA. Comparative review of the adverse effects of treatments for hyerlipidemia. *Drug Safety.* 1991;6(2):118-130.
[147] Hsu I, Spinler SA, Johnson NE. Comparative evaluation of the safety and efficacy of HMG-CoA reductase inhibitor monotherapy in the treatment of primary hypercholesterolemia. *Annals of Pharmacotherapy.* 1995;29:743-759.

SECTION II:

CLINICAL EVIDENCE OF CHOLESTEROL LOWERING WITH ANTI-HYPERLIPIDEMIC DRUGS AND ITS EFFECT ON CHD

Clinical trials of lipid-lowering therapy have demonstrated the relationship between serum cholesterol concentrations and CHD risk over a wide range of cholesterol values. These trials have also shown that decreasing cholesterol levels, decreases CHD mortality and morbidity, slows the progression of CHD and can lead to the regression of atherosclerotic lesions. The trials are categorized as primary prevention trials, secondary prevention trials and angiographic trials. A description of trials under each category follows.

Primary Prevention Trials

Primary prevention includes treating the risk factors (hyperlipidemia) before they cause CHD. Primary prevention trials include patients who are hyperlipidemic but without established CHD. Most of the primary prevention trials (except for AFCAPS/TexCAPS) of lipid-lowering agents included middle-aged men with high cholesterol levels and no CHD. The lipid-lowering agents evaluated in the trials included bile acid resins, fibrates and statins. A total of 21,087 were followed for a period ranging from five to seven years. The treatment with lipid-lowering drugs resulted in a decrease

in LDL levels and triglycerides and an increase in HDL cholesterol levels. These changes in lipid profiles resulted in decreased incidence of CHD. However, cholesterol lowering did not decrease total mortality in most trials and in some trials, this was attributed to lack of statistical power to address the mortality issue. The findings of some of the trials are summarized below.

Primary Prevention Trials of Statin Drugs

Two primary prevention statin trials have shown beneficial effects of the use of these drugs in the primary prevention of CHD. Below is a brief discussion of the trials.

The West of Scotland Coronary Prevention Study (WOSCOPS)

The study was a double-blinded trial in which 6595 men between the ages of 45-64 years with mean plasma cholesterol levels of 272±23 mg/dl were randomly assigned to receive either pravastatin 40mg per day or placebo and were followed for an average of five years. The date of completion of the trial was May 1995. The average age of the patients was 55 years. The objective of the study was to assess the effect of pravastatin on the reduction of combined incidence of non-fatal MI and death from CHD in men with hypercholesterolemia and no history of MI.[148] Pravastatin lowered the plasma levels of

[148] Shepherd J. The West of Scotland Coronary Prevention Study: A Trial of Cholesterol Reduction in Scottish Men. *American Journal of Cardiology.* 1995;76(1):113C-117C.

cholesterol by 20 percent, LDL cholesterol by 26 percent, and triglycerides by 12 percent whereas HDL cholesterol increased by 5 percent.[149]

A 31 percent reduction in non-fatal MI and death from CHD was observed in the pravastatin group as compared with the placebo (95% CI: 17-43%, p<0.001). Treatment with pravastatin was associated with reduced frequency of coronary angiography by 31 percent (95% CI: 10-47%, p=0.007) and revascularization procedures by 37 percent (95% CI: 11-56%, p=0.009). The authors concluded that treatment with pravastatin reduced the incidence of MI and death from CVD in men with hypercholesterolemia.[150]

Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)

This study was a randomized, double-blinded, placebo-controlled trial of men (N=5608) between the ages of 45 to 73 years and postmenopausal women (N=997) between the ages of 55 to 73 years with mildly elevated cholesterol levels.[151] This trial was the first of its kind to assess primary prevention in women and was completed in 1997. The objective of the study was to evaluate the efficacy of 20-40 mg of lovastatin daily, in decreasing the incidence of first major coronary events. Treatment with

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[149] Shepherd J, Cobbe S, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *New England Journal of Medicine.* 1995;333(20):1301-1307.

[150] Shepherd J, Cobbe S, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *New England Journal of Medicine.* 1995;333(20):1301-1307.

[151] Downs JR, Beere PA, Whitney E, et al. Design & Rationale of the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). *American Journal of Cardiology.* 1997;80(3):287-293.

lovastatin reduced the LDL cholesterol by 25 percent and increased HDL cholesterol by 6 percent. The risk for first major coronary event was reduced by 37 percent among subjects treated with lovastatin. The benefits of treatment with lovastatin were observed across all subgroups including women, subjects above the average age of 58 years, diabetics, hypertensives, and those with a family history of CHD. No statistically significant differences were found in the occurrence of CVD and total mortality due to low occurrence of these events in the study population.[152]

Primary Prevention Trials of Other Lipid-Lowering Agents

Two trials have evaluated the effect of cholestyramine and gemfibrozil in the treatment of primary prevention patients. Both trials showed a reduction in major coronary events associated with the use of the lipid-lowering drugs. The results of the trials have been summarized below.

The Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT)

In this study, 3,806 middle aged men aged 35 to 59 years with LDL-C level of 190mg/dl or greater were randomized to receive the lipid-lowering agent cholestyramine 24mg/day or placebo. The main aim of the study was to test the efficacy of lowering

[152] Downs JR, Clearfield M, S W, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels. Results of AFCAPS/TexCAPS. *Journal of the American Medical Association.* 1998;279(20):1615-1622.

cholesterol levels for the primary prevention of CHD.[153] The trial concluded in 1983 and the average period of follow up for the study was 7.4 years. The cholestyramine group showed a decrease in the average plasma total cholesterol and LDL-C reductions of 13.4 percent and 20.3 percent respectively, which was 8.5 percent and 12.6 percent greater compared to the placebo group ($p<0.001$). The combined primary endpoint of definite CHD death and/or definite non-fatal myocardial infarction was 19 percent lower in the treatment group vs. the placebo. This study demonstrated that decrease in the incidence of CHD was primarily due to the reduction of total cholesterol and LDL cholesterol.[154,155]

The Helsinki Heart Study

The study was conducted in the early 1980s and was a five-year randomized, double-blinded, placebo-controlled trial to test the efficacy of the lipid-lowering drug gemfibrozil in reducing the risk of CHD. The mean follow-up period was five years. A total of 4081 middle-aged men with dyslipidemia but initially free of CHD were randomized to receive gemfibrozil 600 mg twice daily or placebo along with recommendations to follow a cholesterol-lowering diet. The mean plasma cholesterol

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[153] Lipid Research Clinic Program Group. The Lipid Research Clinics Coronary Primary Prevention results. I: Reduction in the incidence of coronary heart disease. *Journal of the American Medical Association.* 1984;251(3):351-364.

[154] Lipid Research Clinic Program Group. The Lipid Research Clinics Coronary Primary Prevention results. I: Reduction in the incidence of coronary heart disease. *Journal of the American Medical Association.* 1984;251(3):351-364.

[155] Lipid Research Clinics Program Group. The Lipid Research Clinics Coronary Primary Prevention Trial results. II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. *Journal of the American Medical Association.* 1984;251(3):365-374.

level was 244.7 mg/dl and mean age of the subjects was 47.3 years. LDL cholesterol in the treatment group decreased by 10 percent, total cholesterol decreased by 11 percent and triglycerides decreased by 43 percent. There was an increase in HDL cholesterol by 10 percent. Cardiac end-points in the gemfibrozil group were reduced overall by 34 percent (95% CI: 8.2-52.6). During the study period, the rate of occurrence of cardiac endpoints was lower in the gemfibrozil group (27.3 per 1000) compared to the placebo (41.4 per 1000) ($p<0.02$). No difference in the mortality rates between the two groups was observed. The study showed that treatment with gemfibrozil reduced the incidence of CHD in men with dyslipidemia.[156]

Secondary Prevention Trials

Secondary prevention includes the modification of risk factors to prevent subsequent coronary events in patients with established CHD. Secondary prevention trials include patients who are hyperlipidemic and have established CHD including indications for acute myocardial infarction, angina, chronic ischemic heart disease, history of percutaneous coronary intervention and coronary artery bypass graft. The trials evaluated lipid-lowering agents such as bile acid resins, fibrates, niacin and statins. However, a majority of the trials included statin drugs. A total of 101,036 patients

[156] Frick M, Elo O, Haapa K, et al. Helsinki Heart Study: Primary-prevention trial with Gemfibrozil in middle-aged men with dyslipidemia. *Journal of the American Medical Association.* 1987;317(20):1237-1245.

(62,314 men and 38,722 women) were followed for three to six years except for the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study in which the follow-up period was 16 weeks. Most of the subjects were in their mid-fifties to mid-sixties however, some trials such as the Long-term Intervention with Pravastatin in Ischemic Disease Study (LIPID), Prospective Study of Pravastatin in the Elderly at Risk (PROSPER), Heart Protection Study (HPS) and Women's Health Initiative Trial (WHI) included elderly over 70 years of age. The trials showed that lipid-lowering drugs (mainly statins) can reduce the occurrence of major coronary events such as non-fatal MI and reduce the need for coronary revascularization. In addition, the trials show that lipid-lowering therapy can reduce CHD-related deaths. Some trials such as the HPS, LIPID and the Cholesterol and Recurrent Events (CARE) Study have also shown a reduction in the incidence of stroke in patients treated with statins. Some of the secondary prevention trials including statins and non-statin drugs are summarized below.

Secondary Prevention Trials of Statins

Eight statin trials have been summarized below. The statins evaluated in the trials include simvastatin, pravastatin, and atorvastatin. The results provide evidence of the benefit of statins in the treatment of secondary prevention patients.

The Scandinavian Simvastatin Survival Study (4S)

This study was a randomized, double-blinded, placebo-controlled multicenter clinical trial of 4,444 subjects (men=3,600; women=844) aged 37-70 years with a history of angina pectoris or MI and serum cholesterol of 212-309 mg/dl. Patients were randomly assigned to receive simvastatin or placebo. The mean age of the patients was 58.7 years. The date of completion of the trial was August 1994. After an average follow-up period of 4.7 years, treatment with simvastatin reduced the mean total cholesterol by 25 percent, LDL cholesterol by 35 percent, serum triglycerides by 10 percent and increased HDL cholesterol by 8 percent. The six-year probability of survival in the simvastatin group was higher than in the placebo group (91.3% vs. 87.7%). The relative risk of coronary death and major coronary events was 0.58 (95% CI: 0.46-0.73) and 0.66 (95% CI: 0.59-0.75, $p<0.00001$), respectively.[157] In addition, simvastatin treatment reduced the risk of major coronary events by 34 percent and revascularization procedures by 37 percent.

The authors estimated that with every one percent reduction in LDL cholesterol, level the risk of major coronary events were reduced by 1.7 percent (95% CI: 1.0%-2.4%, $p<0.00001$). There were no major occurrences of side effects in the simvastatin group. The benefits of simvastatin were observed across various subgroups including women, subjects 60 year of age or higher, smokers, diabetics and hypertensives. The authors

[157] Kjekshus J, Berg K, Pedersen TR, et al. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study (4S). *The Lancet.* 1994;344(8934):1383-1389.

concluded that long-term treatment with simvastatin was safe and improved survival in patients with CHD.[158]

The Cholesterol and Recurrent Events Study (CARE)

This study was a double-blinded, placebo-controlled trial of 4,159 subjects (men=3,583; women=576) to evaluate the effect of pravastatin on cholesterol reduction in patients with acute MI and average cholesterol levels of 209 mg/dl. The median follow-up period for the study was five years and the study was completed in February 1996. The mean age of the subjects was 59 $\pm$ 9 years. Treatment with pravastatin reduced the occurrence of CHD related death or non-fatal MI by 24 percent compared to the placebo group.

The incidence of fatal MI reduced by 37 percent whereas the incidence of stroke decreased by 31 percent.[159] The pravastatin group demonstrated a reduction in total serum cholesterol by 20 percent, LDL cholesterol by 32 percent and triglycerides by 14 percent. The HDL levels increased by five percent. The relative risk reduction for the incidence of all types of stroke in the pravastatin group was 32 percent.[160] The authors

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[158] Kjekshus J, Pedersen TR. Reducing the Risk of Coronary Events: Evidence from the Scandinavian Simvastatin Survival Study (4S). *American Journal of Cardiology.* 1995;76(1):64C-68C.

[159] Sacks FM, Moye LA, Davis BR, et al. Relationship between plasma LDL concentrations during treatment with pravastatin and recurrent coronary events in the Cholesterol and Recurrent Events Trial. *Circulation.* 1998;97(15):1446-1452.

[160] Sacks FM, Moye LA, Davis BR, et al. Relationship between plasma LDL concentrations during treatment with pravastatin and recurrent coronary events in the Cholesterol and Recurrent Events Trial. *Circulation.* 1998;97(15):1446-1452.

concluded that treatment with pravastatin led to reduction in coronary events in subjects with average cholesterol levels.

Long-term Intervention with Pravastatin in Ischemic Disease Study (LIPID)

The LIPID study was a multi-center, randomized, placebo-controlled trial of 9,014 patients (men=7,498; women=1,516) aged 31 to 75 years (mean age=61 years) with a history of acute MI or a diagnosis of unstable angina. The subjects were randomized to receive treatment with pravastatin 40mg/day or placebo and were followed for a mean duration of five years. The date of completion of the trial was September 1997. The mean total cholesterol concentration was 220 mg/dl. Pravastatin reduced the risk of occurrence of CHD by 24 percent, risk of total mortality by 23 percent, risk of stroke by 20 percent, risk of occurrence of fatal and non-fatal MI by 29 percent and the need for coronary artery bypass grafting (CABG) by 24 percent.[91] These results were independent of baseline lipid levels. Treatment with pravastatin was associated with a 42 mg/dl fall in LDL cholesterol and a 2.32 mg/dl rise in HDL cholesterol compared with placebo. The authors concluded that treatment with pravastatin therapy was associated with reduced occurrence of coronary events.[161]

Hunt et al. used data from the LIPID trial to further evaluate the effect of pravastatin in older patients between ages 65 to 75 years. Similar effects were observed

[161] Simes RJ, Marschner IC, Hunt D, et al. Relationship Between Lipid Levels and Clinical Outcomes in the Long-Term Intervention With Pravastatin in Ischemic Disease (LIPID) Trial: To What Extent Is the Reduction in Coronary Events With Pravastatin Explained by On-Study Lipid Levels? *Circulation.* 2002;105(10):1162-1169.

in older patients as those observed among younger patients (31 to 64 years).[162] Pravastatin reduced mortality by 21 percent, CHD death or non-fatal MI by 22 percent, stroke by 12 percent, and MI by 26 percent. The authors concluded that pravastatin treatment in older patients reduced the risk for cardiovascular events and mortality.[163]

Tonkin et al.[164] conducted a substudy of the LIPID trial to study the effect of pravastatin on subsequent cardiovascular risks in patients with angina or MI. Among patients treated with placebo, survival for both groups was similar. Among patients treated with pravastatin, the relative risk reduction for mortality was 20.6 percent in the MI group and 26.3 percent in the angina group; however, this difference was not statistically significant. Pravastatin reduced all pre-specified coronary endpoints in the MI group. A number of endpoints in the angina group including CHD mortality, total mortality, MI, coronary revascularization, number as well as length of hospital admissions were significantly lower in the patients treated with pravastatin. The authors concluded that pravastatin provided beneficial effects for patients who have survived acute MI or angina.

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[162] Hunt D, Young P, Simes J, et al. Benefits of pravastatin on cardiovascular events and mortality in older patients with coronary heart disease are equal to or exceed those seen in younger patients: Results from the LIPID trial. *Annals of Internal Medicine.* 2001;134(10):931-940.

[163] Hunt D, Young P, Simes J, et al. Benefits of pravastatin on cardiovascular events and mortality in older patients with coronary heart disease are equal to or exceed those seen in younger patients: Results from the LIPID trial. *Annals of Internal Medicine.* 2001;134(10):931-940.

[164] Tonkin AM, Colquhoun D, Emberson J*, et al.* Effects of pravastatin in 3260 patients with unstable angina: results from the LIPID study. *The Lancet.* 2000;356(9245):1871-1875.

The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Study

The study was a multi-center, randomized, double-blinded trial of 3,086 patients with unstable angina or non-Q-wave acute MI. Patients were followed for an average of 16 weeks to determine if atorvastatin 80 mg/day initiated 24 to 96 hours after an acute coronary syndrome reduced ischemic events. The date of completion of the trial was September 1999. The mean age of the patients was 65 years. The primary end-point in the study was defined as death, non-fatal acute MI, cardiac arrest that needed resuscitation, or symptomatic MI that was recurrent in nature and required urgent rehospitalization. Fewer patients in the atorvastatin group experienced a primary event compared with placebo (14.8% vs. 17.4 %, p=0.048). Recurrent symptomatic MI was significantly reduced in the atorvastatin group compared with placebo (RR=0.74; 95% CI: 0.57-0.95). However, no significant differences were observed between the placebo and the atorvastatin group with respect to death, non-fatal acute MI and cardiac arrest.[165]

[165] Schwartz G, Olsson AG, Ezekowitz M, et al. Effects of Atorvastatin of early recurrent ischemic events in acute coronary syndromes: A randomized controlled trial. *Journal of the American Medical Association.* 2001;285(13):1711-1718.

The Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial (ALLHAT)

The study was a multi-center, randomized, non-blinded trial of 10,355 (men=5,304; women=5,051) hypertensive subjects with moderate hypercholesterolemia with at least one other CHD risk factor. The study concluded in 2002. Mean age of the participants was 66 years and mean cholesterol level was 224 mg/dl. The subjects were randomized to receive either pravastatin 40 mg/day or usual care. All participants were advised to follow a cholesterol lowering diet. Usual care included regular treatment by primary care physicians to lower LDL cholesterol. At the end of four years of follow up, pravastatin treatment lowered the total cholesterol by 17.2 percent and LDL cholesterol by 27.7 percent. No significant differences were found between all cause mortality, stroke and the risk for CHD events between the pravastatin and placebo group. However, pravastatin lowered the relative risk of occurrence of CHD events to a greater extent in blacks compared with non blacks (RR=0.73 vs. 1.02, p=0.03).

The authors attributed the lack of difference in outcomes to the similar cholesterol levels between the two groups and the non-blinded study design.[166] Lack of adherence to pravastatin as evidenced by only 70.3 percent of patients still on therapy at the end of six years as well as increased crossover to lipid-lowering therapies in the usual care group

[166] The ALLHAT Group. Major outcomes in moderately hypercholesterolemic, hypertensive pateints randomized to pravastatin vs. usual care. *Journal of the American Medical Association.* 2002;288(23):2998-2907.

further explained the reason for insignificant findings.[167] The participants in this study represented a unique population as almost half of the participants were females, over one third were black and over half were at least 65 years of age. Moreover, this was the first trial of its kind conducted exclusively among patients treated for hypertension.[168]

Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-lowering Arm (ASCOT-LLA)

This study was a part of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) which was a multi-center, randomized, placebo-controlled trial. In the ASCOT-LLA, 10,305 subjects (men=8,363; women=1,942) with treated hypertension and with at least three cardiovascular risk factors were randomly assigned to receive atorvastatin 10 mg or placebo. The average follow up period was 3.3 years and the study concluded in 2002. The mean age of the participants was 63 years and mean total cholesterol was 213 mg/dl. At the end of a year of treatment, there was a reduction in total cholesterol by 24 percent, LDL cholesterol by 35 percent and triglycerides by 17 percent The atorvastatin group showed a reduction in the occurrence of non-fatal MI and fatal CHD by 36 percent (95% CI: 0.50-0.83, p=0.0005). Revascularization procedures as well as total coronary events were reduced by 21 percent and 29 percent respectively

[167] Pasternak R. The ALLHAT lipid lowering trial - Less is less. *Journal of the American Medical Association.* 2002;288(23):3042-3044.

[168] The ALLHAT Group. Major outcomes in moderately hypercholesterolemic, hypertensive pateints randomized to pravastatin vs. usual care. *Journal of the American Medical Association.* 2002;288(23):2998-2907.

in the atorvastatin group compared to placebo. All-cause mortality did not differ significantly between the two groups. The authors concluded that treatment with atorvastatin led to a reduction in cardiovascular events in hypertensive subjects with average or lower than average cholesterol levels.[169]

Prospective Study of Pravastatin in the Elderly at Risk (PROSPER)

This study was a double-blinded, randomized, placebo-controlled trial to determine the efficacy of pravastatin 40 mg/day in the reduction of cardiovascular and cerebrovascular events in 2,804 elderly men and 3,000 women between 70 to 82 years of age (mean age=75 years) and with vascular disease or at a high risk of developing it.[170] The study concluded in 2002. Pravastatin reduced LDL cholesterol by 34 percent, triglycerides by 12 percent and increased the HDL cholesterol by 5 percent. Coronary events were reduced by 19 percent whereas risk of death due to CHD was reduced by 24 percent in the pravastatin group. The risk of CHD death and non-fatal MI was reduced (Hazard Ratio=0.81; 95% CI: 0.69-0.94, p=0.006). Treatment with pravastatin did not have any effect on the risk reduction for stroke. The authors concluded that pravastatin

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[169] Sever P, Dahlof B, Poulter N, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial- Lipid Lowering Arm (ASCOT-LLA): A multicentre randomised controlled trial. *The Lancet.* 2003;361(9364):1149-1158.

[170] Shepherd J, Blauw G, Murphy M, et al. The design of a prospective study of Pravastatin in the elderly at risk (PROSPER). *American Journal of Cardiology.* 1999;84(10):1192-1197.

reduced the risk of coronary risk in elderly and its use must be promoted to this age group of people.[171]

Heart Protection Study (HPS)

HPS was a secondary prevention randomized placebo-controlled trial of 20,536 (men=15,454; women=5,082) adults aged 40-80 years which concluded in 2001. The mean cholesterol level was 228 mg/dl. Patients were randomized to receive simvastatin 40 mg or placebo as well as vitamin therapy or placebo in a 2 X 2 factorial design for a five-year follow up period.[172] The statin group had a significant reduction in vascular mortality compared with the placebo group (7.6% vs. 9.1%, death rate ratio: 0.83, CI: 0.75-0.91, $p<0.001$). There was a significant reduction of major coronary events including non-fatal MI and coronary death in the simvastatin group vs. the placebo (8.7% vs. 11.8%, $P<0.001$). Similarly, there were significant reduction in the occurrence of non-fatal stroke or fatal stroke (4.3% vs. 5.7%, $p<0.001$) and coronary or non-coronary revascularization (9.1% vs. 11.7%, $p<0.001$) among the simvastatin group vs. the placebo group.[173] The proportional reduction in event rate was observed across all patient

[171] Shepherd J, Blauw G, Murphy J, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): A randomised controlled trial. *The Lancet.* 2002;360(9346):1623-1630.
[172] The Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20536 high-risk individuals: A randomized placebo-controlled trial. *Lancet.* 2002;360(9326):7-22.
[173] The Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20536 high-risk individuals: A randomized placebo-controlled trial. *Lancet.* 2002;360(9326):7-22.

subgroups including the elderly, women and those with non-coronary vascular disease.[174] In this study, there was no difference in the reports of myopathy between the two groups. The findings of the study suggest that more intensive statin treatment is not associated with a marked increase in risk for liver and muscle toxicities.[175]

Secondary Prevention Trials of Other Lipid-lowering drugs

Five trials have been summarized below which include lipid-lowering drugs other than statins such as bezafibrate, gemfibrozil, niacin, clofibrate and estrogen plus progestin therapy. Gemfibrozil reduced the occurrence of major coronary events in the patients. A long-term benefit of niacin was observed in reducing mortality of study subjects. However, bezafibrate, clofibrate and hormone replacement therapy failed to show a significant effect on coronary outcomes in the patients treated with these drugs.

[174] The Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20536 high-risk individuals: A randomized placebo-controlled trial. *Lancet.* 2002;360(9326):7-22.

[175] Ballantyne C M. Current and future aims of lipid-lowering therapy: changing paradigms and lessons from the Heart Protection Study on standards of efficacy and safety. *American Journal of Cardiology.* 2003;92(4B):3K-9K.

The Bezafibrate Infarction Prevention (BIP) Study

This study was a randomized, double-blinded, placebo-controlled trial conducted in Israel. The main aim of the study was to evaluate the efficacy of bezafibrate treatment in the reduction of CHD mortality and non-fatal MI in 3,090 patients (men=2,825; women=265) with a mean age of 60 years and low HDL cholesterol and moderately elevated total cholesterol levels. The subjects were followed for a mean period of 6.2 years and the study concluded in 1999. The mean total cholesterol level was 212 mg/dl. Patients were randomized to receive either 400 mg of bezafibrate or placebo once a day.

The bezafibrate group showed an increase of HDL cholesterol by 18 percent and a decrease in triglycerides by 21 percent. The rate of occurrence of primary endpoint (non-fatal and fatal MI and sudden death) was 13.6 percent and 15.0 percent in the treatment and the placebo group, respectively (p=0.26). At the end of 6.2 years, the cumulative probability of primary endpoint was reduced by 7.3 percent. Rates for non-cardiac and cardiac mortality did not differ between the groups. A post-hoc subgroup analysis of patients with hypertriglyceridemia revealed a significant reduction in coronary events by 39.5 percent. The authors concluded that bezafibrate treatment was effective in elevating HDL cholesterol and decreasing triglyceride levels and there was an overall reduction of clinical endpoints, though it was not statistically significant.[176]

[176] BIP Study Group. Secondary prevention by raising HDL cholesterol and reducing triglycerides in patients with coronary artery disease: The Bezafibrate Infarction Prevention (BIP) Study. *Circulation.* 2000;102(1):21-27.

Veterans Affairs HDL Cholesterol Intervention Trial (VA-HIT)

This study was a randomized, placebo-controlled trial conducted at 20 Veterans Affairs Medical Centers in the mid-1990s. The main aim of the study was to determine the effect of lipid-lowering therapy in the reduction of the incidence of CHD and non-fatal MI in men with low levels of HDL cholesterol and with "desirable" levels of LDL cholesterol.[177] A total of 2,531 men aged less than 73 years and with a mean HDL cholesterol of 32mg/dl and total cholesterol of 175mg/dl were randomized to receive 1200 mg of gemfibrozil or placebo daily. The subjects were followed for a period of approximately six years. The mean age of the patients was 64 years. In patients treated with gemfibrozil, there was an increase in HDL levels by 6 percent, a decrease in triglycerides by 31 percent and no change in LDL levels. A 22 percent reduction in the relative risk in the time to first non- fatal MI or CHD death was observed in the gemfibrozil group (95% CI: 7-35, p=0.006). This study was the first of its kind to show that raising HDL levels and lowering triglyceride levels without changing LDL levels reduced major cardiac events [178]

[177] Rubins H, Robins S, Iwane M, et al. Rationale and design of the department of Veterans Affairs high-density lipoprotein cholesterol intervention trial (HIT) for secondary prevention of coronary artery disease in men with low high-density lipoprotein cholesterol and desirable low-density lipoprotein cholesterol. *American Journal of Cardiology.* 1993;71(1):45-52.

[178] Rubins HB, Robins SJ. Conclusions from the VA-HIT study. *American Journal of Cardiology.* 2000;86(5):543-544.

The Coronary Drug Project (CDP)

The study was a multicenter, randomized, placebo-controlled trial of lipid lowering drugs (clofibrate and niacin) conducted in the 1980s. A total of 8,341 men between the ages of 30-64 years were randomly assigned to the drugs or the placebo and were followed for an average of 6.2 years. The clofibrate group did not show any effect on mortality or non-fatal cardiovascular events. The niacin group experienced a significantly lower incidence of non-fatal MI than the placebo. However, niacin did not have a significant effect on total mortality.[179] Fifteen years of follow up after niacin was discontinued in the study subjects revealed 11 percent lower mortality in this group than the in the placebo group. The authors stated that this delayed benefit of niacin could be attributed to its favorable effect of decreasing non-fatal MI or its lipid-lowering effect or both, early on in the treatment.[180]

Heart and Estrogen/Progestin Replacement Study (HERS)

This study was a randomized, blinded, placebo-controlled trial of 2763 postmenopausal women with CHD and younger than 80 years. The main objective of the study was to determine if estrogen plus progestin therapy reduced the risk of CHD in

[179] Berge KG, Canner P. Coronary Drug Project: experience with niacin. *European Journal of Clinical Pharmacology.* 1991;40(suppl 1):S49-51.
[180] Canner P, Berge K, Wenger N, et al. Fifteen year mortality in Coronary Drug Project patients: long-term benefit with niacin. *Journal of the American College of Cardiology.* 1986;8(6):1245-1255.

postmenopausal women. The subjects were randomized to receive estrogens (0.625 mg) plus progestin (2.5 mg) or placebo. The study concluded in 1998 and at the end of 4.1 years of follow up, there was no difference in primary or secondary cardiovascular outcomes between the two groups.[181] At the end of the first year of the study, LDL cholesterol decreased by 14 percent in the hormone group and three percent in the placebo group ($p<0.001$). There was an increase in the HDL cholesterol by eight percent compared with two percent in the placebo group. Women in the hormone group experienced greater venous thromboembolic events than the placebo group (34 vs. 12, RH=2.89, 95% CI: 1.50-5.58). The rates of occurrence of breast cancer, endometrial cancer and other cancers or fractures did not differ between the two groups. Similarly, the two groups did not differ in total mortality.[182]

The authors concluded that estrogen replacement therapy did not lower the risk of coronary disease among postmenopausal women. Furthermore, an additional follow up of the HERS study women for 6.8 years showed no reduction in risk of cardiovascular disease in women and advised against the use of hormone therapy to reduce risk for CHD events in women.

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[181] Hulley S. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *Journal of the American Medical Association.* 1998;280(7):605-613.

[182] Hulley S. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *Journal of the American Medical Association.* 1998;280(7):605-613.

Women's Health Initiative Trial

This trial was conducted to gain an understanding of the various risks and benefits of strategies to reduce the incidence of heart disease, breast and colorectal cancer, and fractures in postmenopausal women.[183] One arm of this study evaluated the effect of estrogen plus progestin on CHD. The main aim of the study was to assess the effect of estrogen plus progestin on ischemic and hemorrhagic stroke. It was a multi-center, double-blind, placebo-controlled, randomized, clinical trial that concluded in 2002. A total of 16,608 postmenopausal women aged between 50 and 79 years were followed for an average of 5.6 years. Participants were randomized to receive one tablet daily of 0.625 mg of conjugated equine estrogen and 2.5 mg of medroxyprogesterone acetate or placebo.

The occurrence of stroke was 1.8 percent (151 subjects) and 1.3 percent (107 subjects) in the estrogen plus progestin group and placebo group, respectively. The overall hazard ratio for all types of stroke was 1.31 (95% CI: 1.02-1.68). The hazard ratio for all types of strokes was similar across all age groups. There was an increased risk of stroke by 37 percent in women who were part of the estrogen plus progestin group and who had never used hormones prior to participating in the study (Hazard ratio: 1.37; 95% CI: 1.03-1.82). Other risk factors for stroke included ethnicity, current smoking status, hypertension, diabetes, increased white blood cell count, higher hematocrit levels

[183] Rossouw J, Anderson G, Prentice R, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *Journal of the American Medical Association.* 2002 2002;288(3):321-334.

and blood markers for inflammation. The study concluded that estrogen plus progestin increased the risk of stroke in postmenopausal women who were, in general, in good health.[184] Recently published final results of the trial concluded that estrogen plus progestin did not provide protection against cardiac diseases and might increase the risk of coronary heart disease among normally healthy postmenopausal women and recommended against the use of HRT for the prevention of cardiovascular disease.[185]

Angiographic Trials

The use of angiographic techniques to measure the lumen of the coronary arteries and detect small changes in atherosclerotic lesion size led to the evaluation of the effect of cholesterol-lowering therapy in the progression of atherosclerosis. Angiographic trials examined the disease changes based on the progression, regression or no change in angiographic measurements of the coronary arteries.[186] Ten angiographic trials of statin drugs have been discussed below. The statins evaluated in the trials include simvastatin, lovastatin, fluvastatin and pravastatin. A total of 5,440 subjects were followed for a period ranging from two to four years. The mean age of the subjects ranged from 47 to

[184] Smoller-Wassertheil S, Hendrix S, Limacher M, et al. Effect of estrogen plus progestin on stroke in postmenopausal women: The Women's Health Initiative: A randomized trial. *Journal of the American Medical Association.* 2003;289(20):2673-2684.
[185] Manson J, Hsia J, Johnson K, et al. Estrogen plus progestin and the risk of coronary heart disease. *New England Journal of Medicine.* 2003;349(6):523-534.
[186] Rossouw JE. Lipid-Lowering Interventions in Angiographic Trials. *The American Journal of Cardiology.* 1995;76(1):86C-92C.

62 years. The trials have consistently shown that patients have benefited angiographically from long-term statin treatment.

The Simvastatin/Enalapril Coronary Atherosclerosis Trial (SCAT)

This study was a multi-center, randomized, double-blind, placebo-controlled, angiographic trial of cholesterol lowering drug simvastatin and ACE inhibitor enalapril. The purpose of the study was to evaluate the effects of simvastatin and enalapril on coronary atherosclerosis in 460 patients with average cholesterol 201 mg/dl on a total of 460 subjects with a mean age of 61 years. The average follow up period was approximately four years and the study concluded in 1998. All cause mortality and occurrence of cardiovascular events did not differ between the treatment and placebo group. The changes in the coronary angiographic measures included a decrease in mean diameter by 0.07 ± 0.20 in the simvastatin group and 0.14 ± 0.25 mm in the placebo group ($p=0.004$). These differences were not observed in the enalapril group as compared to placebo. Simvastatin patients as compared to placebo required fewer revascularization procedures (6% vs. 12%, $p=0.021$) and angioplasties (3% vs. 9%, $p=0.020$). The occurrence of combined end-points of death, MI and stroke was lower in the enalapril group versus the placebo (7% vs. 13%, $p=0.043$). All cause mortality and clinical events did not differ between the treatment and placebo group. The authors

concluded that lipid-lowering therapy resulted in slowing CHD progression in patients with normal cholesterol levels.[187]

The Monitored Atherosclerosis Regression Study (MARS)

The study was a multi-center, randomized, double-blind, placebo-controlled trial conducted in late 1980s to determine the effect of lovastatin on coronary angiography in 270 patients (male=247; women=63) with CHD and cholesterol levels ranging from 190 mg/dl to 295 mg/dl. The subjects were also recommended a cholesterol lowering diet. Lovastatin treatment reduced the total cholesterol by 32 percent, LDL cholesterol by 38 percent, and apoplipoprotein B by 26 percent, whereas HDL levels were raised by 8.5 percent. For lesions with stenosis of 50 percent or greater at baseline, there was a greater decrease in the diameter of stenosis in the lovastatin group compared with placebo (4.1% vs. 0.9%, p=0.005). Regression of lesions was greater in patients on lovastatin as indicated by a lower global change score as compared with the placebo (0.41 ± 1.14 vs. 0.88 ± 1.12, p=0.02). No differences were observed for coronary events between the two groups. The authors concluded that treatment with lovastatin could slow the rate of progression of coronary artery lesions.[188]

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[187] Teo KK, Burton JR, Buller CE, et al. Long-Term Effects of Cholesterol Lowering and Angiotensin-Converting Enzyme Inhibition on Coronary Atherosclerosis : The Simvastatin/Enalapril Coronary Atherosclerosis Trial (SCAT). *Circulation.* 2000;102(15):1748-1754.

[188] Blankenhorn DH, Azen SP, Kramsch DM, et al. Coronary angiographic changes with lovastatin therapy: The Monitored Atherosclerosis Regression Study (MARS). *Annals of Internal Medicine.* 1993;119(10):969-976.

The Familial Atherosclerosis Treatment Study (FATS)

This study assessed the effects of cholesterol lowering therapy in the regression of CHD in 120 men with a mean age of 47 years and with a high risk of cardiovascular diseases. The study was conducted in the late 1980s. Patients received advice on their diet and were randomly assigned to three treatment groups: lovastatin 20 mg twice a day and colestipol 10 g three times a day; or niacin 1 g four times a day and colestipol or conventional therapy with a placebo. The reduction in LDL cholesterol level was 46 percent in the lovastatin-colestipol group and 32 percent in the niacin-colestipol group. At the end of 2.5 years, the stenosis percent decreased by 0.7 points with the lovastatin-colestipol group and 0.9 points with the niacin-colestipol group ($p<0.003$) whereas it increased by 2.1 points in conventional therapy group. Regression of coronary lesions was three times more common in the treatment group than in the conventional therapy group (p-0.005). Reduction in LDL cholesterol, blood pressure as well as increase in HDL cholesterol correlated individually with the reduction in coronary lesions. The authors concluded that lipid-lowering therapy reduced the progression of coronary lesions in men with CHD and increased risk for cardiovascular events.[189]

[189] Brown G, Albers J, Fisher L, et al. Regression of coronary artery disease as a result of lipid lowering therapy in men with high levels of apolipoprotein B. *New England Journal of Medicine.* 1990;323(19):1289-1298.

The Post Coronary Artery Bypass Graft Trial (Post-CABG trial)

The purpose of this trial was to study the effect of lipid-lowering and low-dose anticoagulation therapy on the progression of atherosclerosis in coronary bypass grafts. A total of 1,351 patients with a mean age of 61.5 years with cholesterol levels between 130 to 175 mg/dl and those who had undergone bypass surgery during a period of one to eleven years prior to the start of the study were included. The study was conducted in the early 1990s. Patients were assigned to aggressive treatment with lovastatin 40 mg/day or moderate treatment with lovastatin 2.5 mg/day and warfarin 1 mg/day or placebo. Based on the cholesterol levels, cholestyramine was added to the lovastatin therapy. The mean duration of follow-up was 4.3 years. Patients who were on aggressive therapy had cholesterol levels ranging from 93 to 97 mg/dl whereas those on moderate treatment, the levels ranged from 132 to 136 mg/dl ($p<0.001$). The mean percentage of grafts with atherosclerosis was 27 percent in the aggressive-treatment group and 30 percent in the moderate-treatment group ($p<0.001$). No significant differences were observed between the warfarin and placebo groups. The authors concluded that aggressive lowering of LDL cholesterol to below 100mg/dl reduced the progression of atherosclerosis in patients who had undergone coronary bypass grafts.[190]

[190] The Post Coronary Artery Bypass Graft Trial Investigators. The effect of aggressive lowering of low-density lipoprotein cholesterol levels and low-dose anticoagulation on obstructive changes in saphenous-vein coronary-artery bypass grafts. *New England Journal of Medicine.* 1997;336(3):153-162.

Lipoprotein and Coronary Atherosclerosis Study (LCAS)

The aim of the study was to assess the effect of fluvastatin on the progression of coronary atherosclerotic lesions and on the development of new coronary lesions in patients with CHD and mild to moderate LDL levels. It was a randomized, double-blind, placebo-controlled trial that concluded in 1996. A total of 429 patients were randomized to receive 20 mg of fluvastatin twice daily or placebo. The mean age of the patients was 57.8 years. Patients whose mean LDL levels pre-randomization was $\geq$ 160 mg/dl were initiated on cholestyramine 12mg/day. Progression of lesions as measured by the minimum lumen diameter was significantly less in the fluvastatin group compared to placebo (-0.028 $\pm$ 0.021 mm vs. -0.100 $\pm$ 0.022 mm, p=0.005). The authors concluded that treatment with fluvastatin slowed the progression of coronary atherosclerosis in patients with mild to moderate LDL levels.[191]

The Regression Growth Evaluation Statin Study (REGRESS)

This study was a double-blind, placebo-controlled, multi-center trial conducted in the early 1990s to evaluate the effect of pravastatin on coronary atherosclerosis. A total of 885 male patients having underwent a coronary arteriography and with a total serum cholesterol level of 155-310 mg/dl were included in the study. Patients were randomized to receive pravastatin 40 mg/day or placebo. The mean segment diameter in the placebo

[191] Herd JA, Ballantyne CM, Farmer JA, et al. Effects of fluvastatin on coronary atherosclerosis in patients with mild to moderate cholesterol elevations (Lipoprotein and Coronary Atherosclerosis Study [LCAS]). *American Journal of Cardiology.* 1997;80(3):278-286.

group decreased by 0.10 mm whereas the decrease in the pravastatin group was 0.06 mm (95% CI: 0.01-0.07, p=0.019). The median decrease in the minimum obstruction diameter in the placebo group was 0.09 mm whereas in the pravastatin the decrease was 0.03 mm (95% CI: 0.02-0.08 mm, p=0.001). The mean intimal-medial thickness values of the common femoral artery decreased by 0.06 mm in the pravastatin group and increased by 0.13 mm in the placebo group (p=0.004). At the end of two years, 89 percent of patients in the pravastatin group and 81 percent of patients in the placebo group were free of clinical events (p=0.002). The authors concluded that treatment with pravastatin had beneficial effects on coronary atherosclerosis and changes in the coronary and peripheral arteries.[192]

Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC I)

The study was randomized, double-blind, placebo-controlled, multi-center trial conducted in the early 1990s to evaluate the effect of pravastatin on the progression of coronary atherosclerosis and ischemic events in patients with coronary artery disease and mild to moderate hyperlipidemia. A total of 408 patients with a mean age of 57 years were randomized to receive pravastatin or placebo for a period of three years. Treatment with pravastatin was associated with a reduction in the progression of atherosclerosis by 40 percent for minimal vessel diameter (p<0.04). Pravastatin also reduced the formation

[192] Groot E, Jukema JW, van Boven J, et al. Effect of pravastatin on progression and regression of coronary atherosclerosis and vessel wall changes in carotid and femoral arteries: A report from the Regression Growth Evaluation Statin Study. *American Journal of Cardiology*. 1995;76(9):40C-46C.

of newer lesions ($p \leq 0.03$). The risk reduction for the occurrence of MI was 60 percent in the pravastatin group ($p \leq 0.05$). The authors concluded that pravastatin reduced the progression of atherosclerosis and myocardial infarction in patients with mild to moderate cholesterol levels and presence of coronary artery disease.[193]

Pravastatin, Lipids, and Atherosclerosis in the Carotid Arteries (PLAC-II)

This was a randomized, double-blind, placebo-controlled trial conducted in the early 1990s to evaluate the effect of pravastatin on the progression of early extracranial carotid atherosclerosis. A total of 151 patients were randomized to receive pravastatin or placebo for a period of three years. The pravastatin group had total cholesterol reduced by 21 percent, LDL cholesterol by 28 percent and triglycerides by 14 percent. Treatment with pravastatin was associated with a 12 percent reduction in the mean carotid artery intimal-medial thickness though this association was not statistically significant. Pravastatin reduced the progression rate in the common carotid artery by 35 percent ($p=0.03$). Pravastatin treatment was associated with a 61 percent reduction in combined endpoint of coronary event and death ($p=0.04$), 80 percent reduction in fatal and non-fatal myocardial infarctions ($p=0.03$). The authors concluded that pravastatin treatment

[193] Pitt B, Mancini GBJ, Ellis S, et al. Pravastatin limitation of atherosclerosis in the coronary arteries (PLAC I): Reduction in atherosclerosis progression and clinical events. *Journal of the American College of Cardiology.* 1995;26(5):1133-1139.

reduced the progression of extracranial atherosclerosis in the common carotid artery and decrease coronary artery events.[194]

Asymptomatic Carotid Artery Progression Study (ACAPS)

This was a randomized, double-blind, placebo-controlled, multi-center clinical trial with a factorial design conducted in the early 1990s. The purpose of the study was to evaluate the effect of lovastatin and/or warfarin on early stage carotid atherosclerosis. A total of 919 men (51.5%) and women between the ages of 40-79 years (mean age=62 years) and no history of cardiovascular disease but having the development of early carotid atherosclerosis were included in the study. Patients were randomized to receive 20-40 mg/day of lovastatin, or lovastatin-placebo and warfarin 1 mg/day or warfarin-placebo over a period of three years. The average follow-up period was 34.1 months. The changes in lipoprotein levels in the lovastatin group were as follows: 17 percent reduction in total cholesterol levels, 28 percent reduction in LDL levels, a five percent reduction in triglyceride levels and a four percent and five percent rise in HDL levels in men and women respectively. Treatment with lovastatin reduced the progression of mean maximum intimal-medial thickness in carotid artery segments ($p<0.001$). Lovastatin treatment as compared to placebo was associated with a reduction in cardiovascular events (5 vs.14 events, $p<0.05$). The authors concluded that treatment with

[194] Byington RP, Furberg CD, Crouse III JR, et al. Pravastatin, lipids, and atherosclerosis in the Carotid Arteries (PLAC-II). *American Journal of Cardiology.* 1995;76(9):54C-59C.

lovastatin reduced the progression of early stage carotid intimal-medial thickness and cardiovascular events in men and women with moderately elevated LDL levels.[195]

The Kuopio Atherosclerosis Prevention Study (KAPS)

The study was a randomized, double-blind, placebo-controlled, primary prevention trial conducted in the early 1990s to evaluate the effect of pravastatin on atherosclerotic progression. A total of 447 men with mean serum cholesterol levels of 189 mg/dl were randomly assigned to pravastatin 40 mg/day or placebo for a period of three years. The mean age of the patients was 57.3 years. The LDL cholesterol level was 29.2 percent lower in the pravastatin group compared to the placebo group. Pravastatin reduced the rate of progression of atherosclerosis in the carotid artery segments by 45 percent (95% CI: 16-69%, p=0.005) and 66 percent in the common carotid arteries (95% CI: 30-90%, p=0.002). The study further provided evidence on the benefits of lowering LDL cholesterol on the reduction on the rate of progression of carotid atherosclerosis in patients who are free of advanced atherosclerosis.[196]

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[195] Probstfield J, Margitic S, Byington RP, et al. Results of the primary outcome measure and clinical events from the asymptomatic carotid artery progression study. *American Journal of Cardiology.* 1995;76(9):47C-53C.

[196] Salonen R, Nyyssonen K, Sarataho E, et al. The Kuopio Atherosclerosis Prevention Study (KAPS): Effect of pravastatin treatment on lipids, oxidation resistance of lipoproteins, and atherosclerotic progression. *American Journal of Cardiology.* 1995;76(9):34C-39C.

Meta-analysis of Primary and Secondary Prevention Trials

Primary and secondary prevention trials have established that cholesterol lowering therapy can reduce CHD events and CHD mortality. However, the effect of treatment on total mortality and non-CHD mortality has been less clear. A majority of the trials have included middle-aged men; thus, the data on women and elderly population is limited. In an attempt to address these issues, several authors have used the meta-analysis technique. Meta-analysis combines the results of individual trials in order to gain a better understanding of the effects of cholesterol lowering therapy on total mortality and in different patient subgroups.

Results of six meta-analyses have been included in this section. These studies pooled the results from both primary and secondary prevention trials of mainly treatment with statins. Based on the results of these studies, treatment with cholesterol-lowering drugs was associated with a reduction in total mortality. Two studies showed the beneficial effects of treatment in reducing the risk of CHD events in women and across different age groups including elderly patients over 65 years.[197,198] The main findings of the studies are discussed below.

[197] Byington RP, Jukema JW, Salonen JT, et al. Reduction in cardiovascular events during pravastatin therapy : Pooled analysis of clinical events of the pravastatin atherosclerosis intervention program. *Circulation.* 1995;92(9):2419-2425.
[198] LaRosa J, Jiang H, Vupputuri S. Effect of statins on risk of coronary disease: A meta-analysis of randomized controlled trials. *Journal of the American Medical Association.* 1999;124(282):2340-2346.

The Prospective Pravastatin Pooling (PPP) project was a pooled analysis of three large randomized trials: the LIPID, CARE and WOSCOPS to assess the effects of pravastatin on total mortality and cause-specific mortality.[199] There was a reduction of fatal or non-fatal MI by 62 percent in the pravastatin group (p=0.001). This was observed across different age groups, gender and in patients with or without histories of hypertension and infarction. The risk for fatal or non-fatal stroke also reduced by 62 percent (p=0.054). The authors concluded that the pooled analysis provided strong support that the risk of cardiac events can be reduced with pravastatin.[200]

LaRosa et al. carried out a meta-analysis of five randomized controlled trials (WOSCOPS, 4S, LIPID, CARE, and AFCAPS/TexCAPS) of statins to evaluate the effect on total mortality and risk of CHD in 30,817 subjects.[201] Statin therapy decreased total cholesterol by 20 percent, LDL cholesterol by 28 percent, triglycerides by 13 percent and increased HDL cholesterol by five percent. Major coronary events were reduced by 31 percent (95% CI: 26%-36%) whereas all-cause mortality was reduced by 21 percent

[199] Simes RJ. Prospective Meta-Analysis of Cholesterol-Lowering Studies: The Prospective Pravastatin Pooling (PPP) Project and the Cholesterol Treatment Trialists (CTT) Collaboration. *American Journal of Cardiology.* 1995;76(1):122C-126C.

[200] Byington RP, Jukema JW, Salonen JT, et al. Reduction in cardiovascular events during pravastatin therapy : Pooled analysis of clinical events of the pravastatin atherosclerosis intervention program. *Circulation.* 1995;92(9):2419-2425.

[201] LaRosa J, Jiang H, Vupputuri S. Effect of statins on risk of coronary disease: A meta-analysis of randomized controlled trials. *Journal of the American Medical Association.* 1999;124(282):2340-2346.

(95% CI: 14%-28%). The risk reduction was similar across gender and among those younger and older than 65 years of age.[202]

Hebert et al. conducted a review of 16 trials including 29,000 subjects to evaluate the effect of statins on the risk of total mortality and stroke.[203] On an average, total cholesterol levels were reduced by 22 percent and LDL levels by 30 percent. The risk reduction for stroke was 29 percent (95% CI: 14%-41%) and for total mortality the risk reduction was 22 percent (95% CI: 16%-37%). Death related to CVD was reduced by 28 percent (95% CI: 16%-37%). Overall, statins were beneficial in the reduction of mortality and stroke.[204]

A meta-analysis conducted by Ross and associates showed a 20 to 30 percent reduction in death or major cardiovascular events with statin treatment compared to placebo.[205] The meta-analysis included 21,303 patients from 17 studies. Statins were effective in reducing adverse cardiovascular outcomes such as stroke, angina and MI. The odds ratio for total mortality was 0.76 (95% CI: 0.67-0.86), for fatal MI the odds

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[202] LaRosa J, Jiang H, Vupputuri S. Effect of statins on risk of coronary disease: A meta-analysis of randomized controlled trials. *Journal of the American Medical Association.* 1999;124(282):2340-2346.

[203] Hebert P, Gaziano M, Chan K, et al. Cholesterol lowering with statins drugs, risk of stroke, and total mortality: an overview of randomized trials. *Journal of the American Medical Association.* 1997;278(4):313-311.

[204] Hebert P, Gaziano M, Chan K, et al. Cholesterol lowering with statins drugs, risk of stroke, and total mortality: an overview of randomized trials. *Journal of the American Medical Association.* 1997;278(4):313-311.

[205] Ross S, Allen E, Connelly J*,* et al. Clinical outcomes in statin treatment trials: a meta analysis. *Archives of Internal Medicine.* 1999;159(15):1793-1802.

ratio was 0.61 (95% CI: 0.48-0.78), and for angina the odds ratio was 0.70 (95% CI: 0.65-0.76) in patients receiving statin therapy.[206]

Law et al. pooled data from 10 prospective studies, three studies conducted in different communities and 28 randomized controlled trials.[207] Based on the results from the cohort studies, a decrease in serum cholesterol concentration by 10 percent (23 mg/dl) was associated with a decrease in incidence of ischemic heart disease by 54 percent at age 40 years, 39 percent at age 50, 27 percent at age 60, 20 percent at age 70, and 19 percent at age 80. The reduction in the risk was 38 percent in the three studies conducted in different communities. There was an overall average reduction of the risk for ischemic heart disease by 18 percent (13%-22%, $p<0.001$) in the randomized controlled trials in men aged 55-64 years. The data for women in the above trials was limited but followed a similar trend.[208] Pooling results from 42 trials of diet and pharmacological intervention showed that cholesterol reduction decreased the total mortality risk in patients with moderate and high CHD risk levels.[209] This association was more predominant among the statin trials than trials with other lipid-lowering drugs.[210]

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[206] Ross S, Allen E, Connelly J, et al. Clinical outcomes in statin treatment trials: a meta analysis. *Archives of Internal Medicine.* 1999;159(15):1793-1802.
[207] Law MR, Wald NJ, Thompson SG. By how much and how quickly does reductionin serum cholesterol concentration lower risk of ischaemic heart disease? *British Medical Journal.* 1994;308(6925):367-373.
[208] Law MR, Wald NJ, Thompson SG. By how much and how quickly does reductionin serum cholesterol concentration lower risk of ischaemic heart disease? *British Medical Journal.* 1994;308(6925):367-373.
[209] Holme I. Cholesterol reduction and its impact on coronary artery disease and total mortality. *The American Journal of Cardiology.* 1995;76(1):10C-17C.
[210] Holme I. Cholesterol reduction and its impact on coronary artery disease and total mortality. *The American Journal of Cardiology.* 1995;76(1):10C-17C.

Cholesterol Reduction and the Risk For Stroke

The relationship between serum cholesterol levels and stroke is unclear and inconsistent. In epidemiologic studies, the incidence of thromboembolic stroke increased with high cholesterol levels but a J-shaped curve was observed due to the inverse relationship between hemorrhagic stroke and cholesterol levels.[211] Meta-analyses of randomized controlled trials of lipid-lowering therapy were conducted to examine the association between cholesterol reduction and the risk for stroke. Of the seven meta-analyses summarized below, three studies included only statin drug trials.[212,213,214]

[211] Neaton JD, Blackburn H, Jacobs D, et al. Serum cholesterol level and mortality findings for men screened in the Multiple Risk Factor Intervention Trial. Multiple Risk Factor Intervention Trial Research Group. *Archives of Internal Medicine.* 1992;152(7):1490-1500.

[212] Warshafsky S, Packard D, Marks S, et al. Efficacy of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors for prevention of stroke. *Journal of General Internal Medicine.* 1999;14(12):763-774.

[213] Crouse III JR, Byington RP, Furberg CD. HMG-CoA reductase inhibitor therapy and stroke risk reduction: an analysis of clinical trials data. *Atherosclerosis.* 1998;138(1):11-24.

[214] Hebert P, Gaziano M, Chan K, et al. Cholesterol lowering with statins drugs, risk of stroke, and total mortality: an overview of randomized trials. *Journal of the American Medical Association.* 1997;278(4):313-311.

Overall, use of statins was associated with a reduced risk for stroke. However, the results of the meta-analyses were mixed with four studies showing a positive association between lipid-lowering and risk of stroke[215,216,217,218] and three studies showing no such effect.[219,220,221]

A meta-analysis conducted by Bucher et al. included 28 primary and secondary trials of statins.[222] There were a total of 49,477 participants in the treatment group and 56,636 participants in the control group. Only those trials that reported the occurrence of fatal or non-fatal strokes were included in the meta-analysis whereas those trials in which patients previously had a stroke were excluded. The reason for this exclusion was that

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[215] Bucher H, Griffith L, Guyatt G. Effect of HMGCoA reductase inhibitors on stroke: A meta-analysis of randomized, controlled trials. *Annals of Internal Medicine.* 1998;128(2):89-95.

[216] Crouse III JR, Byington RP, Furberg CD. HMG-CoA reductase inhibitor therapy and stroke risk reduction: an analysis of clinical trials data. *Atherosclerosis.* 1998;138(1):11-24.

[217] Hebert P, Gaziano M, Chan K, et al. Cholesterol lowering with statins drugs, risk of stroke, and total mortality: an overview of randomized trials. *Journal of the American Medical Association.* 1997;278(4):313-311.

[218] Corvol J, Bouzamondo A, Sirol M, et al. Differential effects of lipid-lowering therapies on stroke prevention. *Archives of Internal Medicine.* 2003;163(6):669-676.

[219] Warshafsky S, Packard D, Marks S, et al. Efficacy of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors for prevention of stroke. *Journal of General Internal Medicine.* 1999;14(12):763-774.

[220] Hebert BJ, Gaziano M, Hennekens CH. An overview of trials of cholesterol lowering and risk of stroke. *Archives of Internal Medicine.* 1995;155(1):50-55.

[221] Atkins D, Psaty B, Koepsell T, et al. Cholesterol reduction and the risk for stroke in men: a meta-analysis of randomized controlled trials. *Annals of Internal Medicine.* 1993;119(2):136-145.

[222] Bucher H, Griffith L, Guyatt G. Effect of HMGCoA reductase inhibitors on stroke: A meta-analysis of randomized, controlled trials. *Annals of Internal Medicine.* 1998;128(2):89-95.

the trials would provide inadequate data on the cause of the stroke. The risk ratio for non-fatal and fatal stroke for subjects on statin therapy was 0.76 (95% CI: 0.62-0.92). The authors concluded that statin therapy reduced the incidence of stroke. However, this effect was not observed with other lipid-lowering agents or dietary interventions.[223]

Warshafsky and colleagues investigated the effect of statins in preventing fatal and non-fatal strokes in patients with high cardiovascular risk.[224] The authors concluded that statins reduced morbidity associated with stroke in patients with high cardiovascular risk. The pooled odds ratio (OR) for total stroke was 0.70 (95% CI: 0.57-0.86, p=0.0005). Only the secondary prevention trials showed a significant risk reduction for total and non-fatal stroke. No association was found between cholesterol reduction and risk for stroke. The authors stated that because of low stroke rates in the trials, the effect of statins on strokes was uncertain.[225]

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[223] Bucher H, Griffith L, Guyatt G. Effect of HMGCoA reductase inhibitors on stroke: A meta-analysis of randomized, controlled trials. *Annals of Internal Medicine.* 1998;128(2):89-95.

[224] Warshafsky S, Packard D, Marks S, et al. Efficacy of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors for prevention of stroke. *Journal of General Internal Medicine.* 1999;14(12):763-774.

[225] Warshafsky S, Packard D, Marks S, et al. Efficacy of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors for prevention of stroke. *Journal of General Internal Medicine.* 1999;14(12):763-774.

Crouse et al. conducted a meta-analysis of 12 studies including primary and secondary prevention trials of statin mono-therapy in the treatment of CHD.[226] A 27 percent reduction in the incidence of stroke was observed in the trials (p=0.001). Meta-analysis of 13 primary or secondary prevention randomized, controlled trials revealed that cholesterol reduction through diet modification or with lipid-lowering agents did not reduce stroke mortality or morbidity in middle-aged men. The odds ratio for fatal stroke associated with interventions to lower cholesterol was 1.32 (95% CI: 0.94-1.86). The odds ratio for non-fatal stroke based on results from eight trials was 0.88 (95% CI: 0.70-0.11).[227]

Hebert and associates investigated whether lipid-lowering with the help of diet, drugs or surgical procedures reduces the risk of stroke.[228] The 17 randomized controlled trials included were either primary prevention, secondary prevention or both primary and secondary prevention trials. Among 36,000 participants, a total of 435 strokes were reported out of which 137 were fatal and 298 were non-fatal. The relative risk for stroke (fatal and non-fatal) in the patients assigned to the treatment group was 1.0 (95% CI: 0.8-1.2) whereas the relative risk for fatal stroke was 1.1 (95% CI: 0.8 to 1.6). The authors

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[226] Crouse III JR, Byington RP, Furberg CD. HMG-CoA reductase inhibitor therapy and stroke risk reduction: an analysis of clinical trials data. *Atherosclerosis.* 1998;138(1):11-24.

[227] Atkins D, Psaty B, Koepsell T, et al. Cholesterol reduction and the risk for stroke in men: a meta-analysis of randomized controlled trials. *Annals of Internal Medicine.* 1993;119(2):136-145.

[228] Hebert BJ, Gaziano M, Hennekens CH. An overview of trials of cholesterol lowering and risk of stroke. *Archives of Internal Medicine.* 1995;155(1):50-55.

concluded that lowering cholesterol did not show any beneficial effect on the risk of stroke and there is a need for large trials to further research this issue. [119] In a separate analysis conducted by Hebert et al. on 16 randomized trials revealed that treatment with statins reduced the risk of stroke by 29 percent (95% CI: 14% -41%). The authors concluded that statins were beneficial in reducing the risk for strokes.[229]

A more recent meta-analysis conducted by Corvol and colleagues that included 38 trials and 83,161 patients revealed that lipid-lowering treatment lowered the relative risk of stroke by 17 percent.[230] Statin trials as well as secondary prevention trials had the best relative risk reduction of the incidence of stroke. The relative risk reduction of stroke incidence was significantly associated with cholesterol reduction ($r=0.46$, $p<0.001$). This was true when cholesterol levels were reduced to less than 232 mg/dl.[231]

Summary

Primary, secondary and angiographic trials have demonstrated the beneficial effects of lipid-lowering drugs especially statins in the reduction of CHD associated mortality and morbidity. These benefits have been observed irrespective of the age group, cholesterol levels, various CHD risk factors and in the presence or absence of

[229] Hebert BJ, Gaziano M, Hennekens CH. An overview of trials of cholesterol lowering and risk of stroke. *Archives of Internal Medicine.* 1995;155(1):50-55.
[230] Corvol J, Bouzamondo A, Sirol M, et al. Differential effects of lipid-lowering therapies on stroke prevention. *Archives of Internal Medicine.* 2003;163(6):669-676.
[231] Corvol J, Bouzamondo A, Sirol M, et al. Differential effects of lipid-lowering therapies on stroke prevention. *Archives of Internal Medicine.* 2003;163(6):669-676.

prior CHD. Given the beneficial effects of statin therapy in the prevention of CHD, compliance with these drugs is an important issue in the management of hyperlipidemia.

SECTION III

COMPLIANCE WITH LIPID-LOWERING THERAPY

Compliance

Compliance is defined as "the extent to which a person's behavior (in terms of taking medications, following diets, or executing lifestyle changes) coincides with medical or health advice."[232] Other terms used to denote compliance include adherence, obedience, cooperation, concordance, collaboration and therapeutic alliance.[233] The term 'adherence' is most often interchangeably used with the term "compliance." This is mainly due to the concern that the term compliance is associated with negative connotation since the patient is considered to be submissive to the doctor's orders to comply with the medication regimen.[234] The measures of compliance for the purpose of this study include adherence and persistence. Adherence refers to "how well a patient follows physician orders within a designated time frame" whereas persistence "addresses

[232] Haynes RB. Introduction. In: Sackett DL, ed. *Compliance in Health Care*: The Johns Hopkins University Press, Baltimore and London; 1979:1-10.
[233] DiMatteo MR, DiNicola DD. The compliance problem: An introduction. In: DiNicola DD, ed. *Achieving Patient Compliance: The Psychology of the Medical Practitioner's Role*. New York: Pergamon Press Inc.; 1982:1-27.
[234] Haynes RB. Introduction. In: Sackett DL, ed. *Compliance in Health Care*: The Johns Hopkins University Press, Baltimore and London; 1979:1-10.

how long a patient remains on therapy."[235] For the purpose of this research, compliance with statins will be assessed with the help of adherence and persistence to therapy.

Variability in patient compliance to the prescribed medication regimen can have a crucial effect on the drug response as well as alter the number of patients required to detect a difference between the treatment and the placebo group.[236,237] In addition, non-compliance can decrease the overall effectiveness of interventions and increase the health care costs.[238] The economic costs of medication non-adherence exceed $100 billion annually including the costs of hospitalizations, nursing home admissions, lost productivity, premature deaths and treatments.[239]

Patients can be non-compliant with their medication regimens for a number of reasons including lack of understanding of the need for medication, especially in asymptomatic conditions such as hyperlipidemia.[240] Moreover, complexity of medication

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[235] Dezii C. Persistence with drug therapy: A practical approach using administrative claims data. *Managed Care.* 2001;10(2):42-45.
[236] Urquhart J. Pharmacoeconomic consequences of variable patient compliance with prescribed drug regimens. *Pharmacoeconomics.* 1999;15(3):217-228.
[237] Farmer KC. Methods for measuring and monitoring medication regimen adherence in clinical trials and clinical practice. *Clinical Therapeutics.* 1999;21(6):1074-1090.
[238] Cleemput I, Kesteloot K. Economic implications of non-compliance in health care. *Lancet.* 2002;359(9324):2129-2130.
[239] National Pharmaceutical Council. Emerging issues in pharmaceutical cost containment. Reston, VA. 1992;2(2):1-16.
[240] Miller N. Compliance with treatment regimens in chronic asymptomatic diseases. *American Journal of Medicine.* 1997;102(2A):43-49.

regimens, side effects of the drugs and the cost of medications also contribute to lack of compliance with medication regimens.[241]

Measures of Non-Compliance

Non-compliance with drug therapy can be evaluated through indirect methods such as pill counts, medication refill rates, self-reports, interviews, electronic monitoring devices or direct methods such as biologic markers, presence of drug or its metabolite in the body fluids, and direct observation of patient taking the medication.[242,243]

Direct methods are more reliable in assessing compliance, however; they may not be practical in most situations and might be considered invasive. Moreover, in retrospective database studies such as this research, it would be nearly impossible to obtain the direct measurements of non-compliance unless laboratory tests were part of the database.

Indirect methods are most often used to measure compliance and have some advantages and disadvantages. Indirect methods of collecting non-adherence information are relatively inexpensive and noninvasive. However, they are less reliable than direct

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[241] Coombs JH, Cornish L, Hiller P, et al. Compliance and refill pattern behavior with HMG-CoA reductase inhibitors after acute myocardial infarction. *Managed Care Interface.* 2002;15(1):54-58.
[242] Farmer KC. Methods for measuring and monitoring medication regimen adherence in clinical trials and clinical practice. *Clinical Therapeutics.* 1999;21(6):1074-1090.
[243] Bond WS, Hussar DA. Detection methods and strategies for improving medication compliance. *American Journal of Health System Pharmacy.* 1991;48(9):1978-1988.

methods.[244] For example, pill counts can verify the quantity of medication removed from the bottle but cannot verify the correct timing of doses or the actual taking of medications.[245]

Pill counts have been found to overestimate the patient's actual compliance behavior since the patient might not return all the pills in order to conceal their non-compliant behaviors.[246] Completion of self-reports or patient diaries are burdensome on the patients. It might not capture the patient's medication taking behavior and could be subjected to recall bias. Electronic monitoring devices offer an unobtrusive and convenient method to track the quantity and the timing of doses but the devices may be costly. Moreover, there is no way to verify if the dose was actually consumed.[247]

Measuring compliance based on prescription refill records has been commonly used in retrospective database analysis. However, prescription refill limits such as those in the Texas Medicaid program can hamper the compliance measures since only those claims that are covered will appear in the database and those that are not covered will be missing from the database. In addition to the pharmacy claims data, researchers must

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[244] Bond WS, Hussar DA. Detection methods and strategies for improving medication compliance. *American Journal of Health System Pharmacy.* 1991;48(9):1978-1988.
[245] Choo PW, Rand CS, Inui TS, et al. Validation of patient reports, automated pharmacy records, and pill counts with electronic monitoring of adherence to antihypertensive therapy. *Medical Care.* 1999;37(9):846-857.
[246] Farmer KC. Methods for measuring and monitoring medication regimen adherence in clinical trials and clinical practice. *Clinical Therapeutics.* 1999;21(6):1074-1090.
[247] Choo PW, Rand CS, Inui TS, et al. Validation of patient reports, automated pharmacy records, and pill counts with electronic monitoring of adherence to antihypertensive therapy. *Medical Care.* 1999;37(9):846-857.

have access to the eligibility file to verify continuous eligibility which would help in differentiating between non-compliance and drop-outs from the insurance plans.[248] Steiner et al. published a review of methodologies to assess compliance and found a significant correlation between refill compliance and other compliance behaviors such as appointment-keeping or consumption of medication.[249] Moderate association was found between compliance measures and drug plasma levels and blood pressure control. The authors concluded that assessing prescription refills based on pharmacy records is a useful source for measuring compliance when direct measurements of compliance are not feasible.[250] In summary, there is no 'perfect' method to measure compliance to medication regimens. There exists a trade-off between complete reliability of the measures versus the practicality in terms of time, money and ease in obtaining the measures.

[248] Choo PW, Rand CS, Inui TS, et al. Validation of patient reports, automated pharmacy records, and pill counts with electronic monitoring of adherence to antihypertensive therapy. *Medical Care.* 1999;37(9):846-857.
[249] Steiner J, Prochazka A. The assessment of refill compliance using pharmacy records: Methods, validity and applications. *Journal of Clinical Epidemiology.* 1997;50(1):105-116.
[250] Steiner J, Prochazka A. The assessment of refill compliance using pharmacy records: Methods, validity and applications. *Journal of Clinical Epidemiology.* 1997;50(1):105-116.

Impact of the Variable Compliance on CHD Outcomes

Adherence with cholesterol-lowering therapy plays an important role in the achievement of NCEP goals.[251] Poor adherence is more frequent in treatments that are preventive than curative. Hyperlipidemia is a chronic, painless condition that is perceived by patients to have harmful effects sometime in the future. Moreover, primary prevention CHD patients who have not yet experienced a CHD event would be more likely to be non-adherent than secondary prevention patients. For example, in primary prevention trials, such as WOSCOPS, the discontinuation rates were 30 percent in five years whereas in secondary prevention trials, such as 4S, the rate was 10 percent in five years.[252] Patient adherence to the drug regimen is of paramount importance since statin therapy could be a life-long therapy. However, discontinuation rates of anti-hyperlipidemic agents are high, ranging from 10 to 60 percent.[253] Appropriate dosing and titration of lipid-lowering agents is required in order to attain lipid goals.

There have been very few studies in the literature that have examined the impact of medication compliance on CHD outcomes. McDermott and his colleagues conducted a literature review to examine the impact of non-adherence to medication on CHD

[251] Harley CR, Setareh WA, McDonough KL, et al. Cholesterol management in a population of managed care enrollees. *Journal of Clinical Outcomes Management.* 2003;10(3):147-154.
[252] Insull W. The problem of compliance to cholesterol altering therapy. *Journal of Internal Medicine.* 1997;241(4):317-325.
[253] Hughes D, Bagust A, Haycox A, et al. Accounting for noncompliance in pharmacoeconomics. *Pharmacoeconomics.* 2001;19(12):1185-1197.

mortality and morbidity. [254] The authors studied the impact of medication adherence on survival, hospitalization and readmission. Twenty research articles met their inclusion criteria. These articles included patients with CHD or MI (6 trials), congestive heart failure (9 trials), hypertension (2 trials), hypercholesterolemia (1 trial), and CHD (2 trials). The studies used different definitions of adherence and different methods of adherence measurements. The authors could not identify any randomized clinical trials that specifically evaluated the effect of compliance with medication regimen on CHD outcomes. There were three clinical trials that included strategies to improve medication adherence as part of an intervention to reduce hospitalization and/or mortality in elderly congestive heart failure patients. Of these, two trials showed a positive impact of the intervention on mortality and morbidity. Six studies compared hospitalization rates between adherent and non-adherent patients; of these, three studies showed a significant impact of adherence on hospitalization. Out of seven studies that assessed the impact of adherence on mortality, four studies showed a favorable impact of adherence on survival.

The review also included findings from lipid-lowering trials such as the Coronary Drug Project Research (CDRP) and the Lipid Research Clinics Primary Prevention trial (LRCPPT) that described the impact of compliance with lipid-lowering drugs on mortality. In the LRCPPT a 10 percent reduction in LDL levels was associated with

[254] McDermott M, Schmitt B, Wallner E. Impact of medication nonadherence on coronary heart disease outcomes: A critical review. *Archives of Internal Medicine.* 1997;157(17):1921-1928.

patient compliance with cholestyramine.[255] In the CDRP study, the 5-year mortality rates were lower for patients who were adherent 80 percent or more to their clofibrate drug regimen than those who were not. However, similar findings were observed in the placebo group as well.[256] Patients in the WOSCOPS trial who were 75 percent adherent with statin therapy had a 50 percent higher reduction in cardiovascular risk than those who were not adherent.[257] In summary, few studies have determined the impact of medication compliance on CHD outcomes. Medication compliance has been associated with improved CHD outcomes in the majority of the studies included in the meta-analysis. Despite very few studies of the impact of compliance on CHD outcomes, a number of studies have assessed the compliance of lipid-lowering agents in primary care settings. The next section provides an overview of a summary of the findings of these studies.

Compliance with Lipid-lowering Drugs in Primary Care Settings

There were seven studies that assessed compliance with lipid-lowering drugs, mainly statins, in primary care settings. Three studies used data from health maintenance

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[255] Lipid Research Clinic Program Group. The Lipid Research Clinics Coronary Primary Prevention results. I: Reduction in the incidence of coronary heart disease. *Journal of the American Medical Association.* 1984;251(3):351-364.

[256] Coronary Drug Project Research Group. Influence of adherence to treatment and response of cholesterol on mortality in the Coronary Drug Project. *New England Journal of Medicine.* 1980;303(18):1038-1041.

[257] West of Scotland Coronary Prevention Study Group. Influence of pravastatin and plasma lipids on clinical events in the West of Scotland Coronary Prevention Study (WOSCOPS). *Circulation.* 1998;97(15):1440-1445.

organizations (HMOs),[258,259,260] two studies used the New Jersey Medicaid data,[261,262] one study used data from a preventive cardiology service[263] and one study examined population-based administrative data from Ontario.[264] These studies highlight the lack of compliance to lipid-lowering therapy in clinical practice and increased discontinuation of drugs with time.

The discontinuation rates of antihyperlipidemic agents in HMO settings are higher than those reported in clinical trials. For example, the discontinuation rates after one year of treatment in the HMO settings was 41 percent for bile acid sequestrants, 46 percent for niacin, 15 percent for lovastatin and 37 percent for gemfibrozil. In a randomized clinical trial, discontinuation rates (except for lovastatin) were lower with 31 percent for bile acid

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[258] Andrade S, Walker AM, Gottolieb L, et al. Discontinuation of antihyperlipidemic drugs-do rates reported in clinical trials reflect rates in primary care settings? *New England Journal of Medicine.* 1995;332(17):1125-1131.

[259] Sung JCY, Nichol MB, Venturini F*,* et al*.* Factors affecting patient compliance with antihyperlipidemic medication in an HMO population. *American Journal of Managed Care.* 1998;4(10):1421-1430.

[260] Andrade SE, Saperia GM, Berger ML, et al. Effectiveness of antihyperlipidemic drug management in clinical practice. *Clinical Therapeutics.* 1999;21(11):1973-1987.

[261] Benner J, Glynn R, Mogun H*, et al.* Long-term persistence in use of statin therapy in elderly patients. *Journal of the American Medical Association.* 2002;288(4):455-461.

[262] Avorn J, Monette J, Lacour A, et al. Persistence of the use of lipid lowering medications: A cross national study. *Journal of the American Medical Association.* 1998;279(18):1458-1452.

[263] Frolkis JP, Pearce GL, Nambi V*,* et al*.* Statins do not meet expectations for lowering low-density lipoprotein cholesterol levels when used in clinical practice. *American Journal of Medicine.* 2002;113(8):625-629.

[264] Jackevicius C, Mamdani M, Tu J. Adherence with statin therapy in elderly patients with and without acute coronary syndromes. *Journal of the American Medical Association.* 2002;288(4):462-467.

sequestrants, four percent for niacin and 15 percent for gemfibrozil.[265] LDL cholesterol reduction in clinical practice was also observed to be lower than projected in the package inserts of the drugs mainly due to non-compliance.[266] In a retrospective HMO study conducted by Sung et al., only 37 percent of participants adhered to their lipid-lowering therapy throughout the study period.[267] In another study of HMO patients, only 62 percent of the therapies were continued at the end of six months and 21 percent at the end of two years.[268]

Two studies showed a decline in adherence to statin therapy among the elderly. Jackevicius et al. reported that at the end of two years, the adherence to statins was 36.1 percent for elderly patients with chronic CHD and 25.4 percent for primary prevention patients.[269] A retrospective cohort study of enrollees in the New Jersey Medicaid program showed that adherence to statin therapy declined with time. The proportion of days covered by statin therapy decreased from 79 percent in the first three months of

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[265] Andrade S, Walker AM, Gottolieb L, et al. Discontinuation of antihyperlipidemic drugs-do rates reported in clinical trials reflect rates in primary care settings? *New England Journal of Medicine.* 1995;332(17):1125-1131.

[266] Frolkis JP, Pearce GL, Nambi V*,* et al*.* Statins do not meet expectations for lowering low-density lipoprotein cholesterol levels when used in clinical practice. *American Journal of Medicine.* 2002;113(8):625-629.

[267] Sung JCY, Nichol MB, Venturini F*,* et al*.* Factors affecting patient compliance with antihyperlipidemic medication in an HMO population. *American Journal of Managed Care.* 1998;4(10):1421-1430.

[268] Andrade SE, Saperia GM, Berger ML, et al. Effectiveness of antihyperlipidemic drug management in clinical practice. *Clinical Therapeutics.* 1999;21(11):1973-1987.

[269] Jackevicius C, Mamdani M, Tu J. Adherence with statin therapy in elderly patients with and without acute coronary syndromes. *Journal of the American Medical Association.* 2002;288(4):462-467.

treatment to 42 percent after 120 months.[270] Another study of elderly patients on statins in the New Jersey Medicaid and the Quebec medical care program showed that at the end of one year, patients failed to fill the prescriptions 40 percent of the time and five years later only half the patients were still getting their prescription filled. Persistence rates with statins were higher than those with other lipid-lowering agents, particularly with bile acid sequestrants, cholestyramine and colestipol. Patients with hypertension, diabetes and CHD had better adherence to therapy than those without these risk factors.[271]

In summary, compliance with lipid-lowering drugs in primary care setting is an issue of concern since compliance with statin therapy decreases over time in hyperlipidemic patients including elderly patients, especially those with CHD and with established risk factors. In order to improve patient compliance with lipid-lowering medications in clinical practice, it is vital to gain an understanding of the various factors that affect compliance.

Factors Affecting Compliance with Lipid-Lowering Drugs

A number of factors affect compliance with drug therapy. Studies have evaluated the factors that affect compliance with lipid-lowering drugs. A brief description of the study results is given below.

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[270] Benner J, Glynn R, Mogun H, et al. Long-term persistence in use of statin therapy in elderly patients. *Journal of the American Medical Association.* 2002;288(4):455-461.
[271] Avorn J, Monette J, Lacour A, et al. Persistence of the use of lipid lowering medications: A cross national study. *Journal of the American Medical Association.* 1998;279(18):1458-1452.

Factors inversely associated with compliance include occurrence of side-effects with the lipid-lowering therapy, high number of prescription medications, smoking status, break in physician visits, young age, female gender, and presence of comorbidities. [272,273,274] Other factors that negatively affected compliance with statin therapy include days' supply of medications, number of concomitant medications and copayment.[275] Factors positively associated with compliance include increased physician-patient interaction regarding cholesterol and cardiovascular disease and patient's perception about the efficacy of lipid-lowering drugs in preventing cardiovascular diseases.[276] Predictors of poor compliance with statins among elderly include nonwhite race, lower income, older age, less cardiovascular morbidity at initiation of therapy, depression, dementia, and occurrence of coronary heart disease

[272] Kiortsis D, Giral P, Bruckert E, et al. Factors associated with low compliance with lipid-lowering drugs in hyperlipidemic patients. *Journal of Clinical Pharmacy & Therapeutics*. 2000;25(6):445-451.
[273] Sung JCY, Nichol MB, Venturini F, et al. Factors affecting patient compliance with antihyperlipidemic medication in an HMO population. *American Journal of Managed Care*. 1998;4(10):1421-1430.
[274] Ellis JJ, Erickson SR, Stevenson JG, et al. Suboptimal statin adherence and discontinuation in primary and secondary prevention populations. *Journal of General Internal Medicine*. 2004;19(6):638-645.
[275] Coombs JH, Cornish L, Hiller P, et al. Compliance and refill pattern behavior with HMG-CoA reductase inhibitors after acute myocardial infarction. *Managed Care Interface*. 2002;15(1):54-58.
[276] Kiortsis D, Giral P, Bruckert E, et al. Factors associated with low compliance with lipid-lowering drugs in hyperlipidemic patients. *Journal of Clinical Pharmacy & Therapeutics*. 2000;25(6):445-451.

events after initiation of therapy.[277] In an elderly Medicaid population, age, ethnicity and severity of CHD were significant predictors of persistence to statin therapy. [278]

Bruckert et al. conducted an open-label study in hyperlipidemic patients to evaluate three objectives: to assess compliance with fluvastatin; to understand the relationship between treatment compliance and sociodemographic, clinical and psychological factors; and to evaluate the effect of raising patient awareness through the distribution of information.[279] The control group received regular information from their physician, whereas the treatment group received information on diet and role of cholesterol in coronary heart disease. A majority of the patients (75 percent, 2,888/3,845) were compliant with therapy (i.e., they filled more than 90 percent of fluvastatin prescriptions). Both of the groups were similar with respect to demographic characteristics and different risk factors with the exception of diabetes. The non-compliant group had a higher occurrence of adverse events compared with the compliant group (10% vs. 3.4%, p=0.001). In the non-compliant group, there were a large number

[277] Benner J, Glynn R, Mogun H, et al. Long-term persistence in use of statin therapy in elderly patients. *Journal of the American Medical Association.* 2002;288(4):455-461.
[278] Benner J, Glynn R, Mogun H, et al. Long-term persistence in use of statin therapy in elderly patients. *Journal of the American Medical Association.* 2002;288(4):455-461.
[279] Bruckert E, Simonetta C, Giral P. Compliance with fluvastatin treatment characterization of the noncompliant population within a population of 3845 patients with hyperlipidemia. *Journal of Clinical Epidemiology.* 1999;52(6):589-594.

of symptomatic patients who thought that the drug did not improve the symptoms (17.1% vs. 20.3%, p=0.005).[280] Muhlestein and colleagues reported that prescription of statin therapy at the time of hospital discharge following an angiographic diagnosis of CHD was a predictor of long-term statin compliance as well as reduced mortality.[281]

Summary

Lack of compliance with lipid-lowering medications is an issue of concern in the treatment of hyperlipidemia. The literature reports a decrease in compliance with drug regimens with time. Despite the literature lacking in studies assessing the impact of medication compliance on CHD outcomes, some studies have shown poor CHD outcomes in non-compliant patients. Lack of compliance with statin drug regimens have been associated with ineffective management of hyperlipidemia in primary care settings.

[280] Bruckert E, Simonetta C, Giral P. Compliance with fluvastatin treatment characterization of the noncompliant population within a population of 3845 patients with hyperlipidemia. *Journal of Clinical Epidemiology.* 1999;52(6):589-594.

[281] Muhlestein JB, Horne BD, Bair TL, et al. Usefulness of in-hospital prescription of statin agents after angiographic diagnosis of coronary artery disease in improving continued compliance and reduced mortality. *American Journal of Cardiology.* 2001;87(3):257-261.

SECTION IV

LIPID MANAGEMENT IN PRIMARY CARE SETTINGS AND IN SPECIAL POPULATIONS

Lipid Management in Primary Care Settings

Under-diagnosis and under-treatment of hyperlipidemia in "real-world settings" are contributors to the failure to achieve NCEP treatment goals. Under-utilization of lipid-lowering therapy could be attributed to the relatively expensive cost of drugs as well as long-term duration of treatment.[282] Despite the presence of the NCEP guidelines for cholesterol management, there exists a gap between the guidelines and its implementation in clinical practices. A number of studies provide support for the lack of translation of lipid-lowering benefits observed in clinical trials to practice settings.

Andrade et al. attributed the lack of positive association between the use of antihyperlipidemic agents and CHD hospitalization to discontinuation of therapy or failure to achieve the LDL goals while on therapy.[283] In a retrospective analysis of data for 48,586 patients, 61 percent of CHD patients were not treated with lipid-lowering

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[282] Lai L, Poblet M, Bello C. Are patients with hyperlipidemia being treated? Investigation of cholesterol treatment practices in an HMO primary care setting. *Southern Medical Journal.* 2000;93(3):283-286.

[283] Andrade SE, Saperia GM, Berger ML, et al. Effectiveness of antihyperlipidemic drug management in clinical practice. *Clinical Therapeutics.* 1999;21(11):1973-1987.

agents.[284] The Lipid Treatment Assessment Project (L-TAP) which evaluated the percent of hyperlipidemic patients on lipid-lowering therapy and achieving LDL goals showed that overall only 38 percent of the patients on drug therapy achieved LDL goals and the success rates were lowest for high-risk patients and those with CHD.[285]

Pearson et al. stated that there is gap between NCEP guidelines and attainment of goals in clinical settings and cited a few studies supporting this.[286] For example, in the Heart and Estrogen/Progestin Replacement Study, only 47 percent of eligible patients were on lipid-lowering drugs and 63 percent of the patients did not achieve the LDL target levels.[287] In a study conducted at a Veterans Affairs Medical Center, only 33 percent of the patients achieved the LDL goals. Factors affecting the achievement of lipid goals included lower baseline LDL levels and triglyceride levels, use of combination drug therapy, and patient adherence to therapy.[288] Based on a study in a German outpatient population, lack of implementation of treatment guidelines was

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[284] Sueta C, Massing M, Chowdhury M, et al. Undertreatment of hyperlipidemia in patients with coronary artery disease and heart failure. *Journal of Cardiac Failure.* 2003;9(1):36-41.

[285] Pearson T, Laurora I, Chu H, et al. The Lipid Treatment Assessment Project (L-TAP): A multicenter survey to evaluate the percentages of dyslipidemic patients receiving lipid-lowering therapy and achieving low-density lipoprotein cholesterol goals. *Archives of Internal Medicine.* 2000;160(4):459-467.

[286] Pearson T. The undertreatment of LDL-cholesterol: Addressing the challenge. *International Journal of Cardiology.* 2000;74(suppl 1):S23-S28.

[287] Schrott H, Bittner V, Vittinghoff E, et al. Adherence to National Cholesterol Education Program treatment goals in postmenopausal women with heart disease: the Heart and Estrogen/Progestin Replacement study. *Journal of the American Medical Association.* 1997;277(16):1281-1286.

[288] Schectman G, Hiatt J. Drug therapy for hypercholesterolemia in patients with cardiovascular disease: Factors limiting achievement of lipid goals. *American Journal of Medicine.* 1996;100(2):197-204.

observed in which only 6.2 percent of a total of 2,856 CHD patients were found to meet the target LDL levels.[289]

A retrospective analysis of data from a national managed care organization showed that only 43 percent (12,781/29,534) of eligible patients were on statin therapy.[290] Of these, only 46 percent continued statin therapy at the end of two years. Over half (59 percent) had one or more cholesterol monitoring tests during the two year study period. Statin users (OR=1.78, 95% CI: 1.23-2.56) with a higher rate of compliance (OR=2.09, 95% CI: 1.32-3.31) were more likely to attain the NCEP goals compared with non-statin users with lower compliance rate.[291] The problem of under-treatment is also evident in the NHANES where 82.5 percent of patients with CHD and over half of those without CHD and with greater than two risk factors were not meeting the treatment goals.[292] The recently conducted Genetic Epidemiology Network of Arteriopathy study concluded that less than one-third of the hypertensive patients in the study were treated for hyperlipidemia and fewer than half of these were attaining the lipid

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[289] Ruof J, Klein G, Marz W, et al. Lipid-lowering medication for secondary prevention of coronary heart disease in a German outpatient population: The gap between treatment guidelines and real life treatment patterns. *Preventive Medicine.* 2002;35(1):48-53.

[290] Harley CR, Setareh WA, McDonough KL, et al. Cholesterol management in a population of managed care enrollees. *Journal of Clinical Outcomes Management.* 2003;10(3):147-154.

[291] Harley CR, Setareh WA, McDonough KL, et al. Cholesterol management in a population of managed care enrollees. *Journal of Clinical Outcomes Management.* 2003;10(3):147-154.

[292] Hoerger TJ, Bala MV, Bray JW, et al. Treatment patterns and distribution of low-density lipoprotein cholesterol levels in treatment-eligible United States adults. *American Journal of Cardiology.* 1998;82(1):61-65.

goals. Moreover, nine out of 10 hypertensive patients with hyperlipidemia were not adequately treated for hyperlipidemia.[293]

Lack of Physician Adherence to Guidelines

Screening and treatment of hyperlipidemia is a crucial component in the primary and secondary prevention of CHD. Physician compliance with cholesterol management guidelines is limited.[294] Hyperlipidemic patients are counseled on cholesterol management at a mean rate of only 34 percent annually which translates to once every three years. Cholesterol counseling is more likely in the presence of cardiovascular diseases and related risk factors such as diabetes, hypertension and obesity.[295]

Yarzebski et al. conducted a survey of physicians in 1999 to evaluate their attitudes towards cholesterol management in patients with acute MI.[296] Lipid-lowering therapy was more likely to be initiated in younger patients at lower cholesterol levels than older patients (p=0.03). Older physicians were likely to adhere to recommended guidelines to cholesterol management than younger physicians. A majority of the

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[293] O'Meara JG, Kardia SL, Armond JJ, et al. Ethnic and sex differences in the prevalence, treatment, and control of dyslipidemia among hypertensive adults in the GENOA study. *Archives of Internal Medicine.* 2004;164(12):1313-1318.

[294] Stafford RS, Blumenthal D, Pasternak R. Variations in cholesterol management practices of U.S physicians. *Journal of the American College of Cardiology.* 1997;29(1):139-146.

[295] Stafford RS, Blumenthal D, Pasternak R. Variations in cholesterol management practices of U.S physicians. *Journal of the American College of Cardiology.* 1997;29(1):139-146.

[296] Yarzebski J, Bujor CF, Goldberg RJ, et al. A community-wide survey of physician practices and attitudes toward cholesterol management in patients with recent acute myocardial infarction. *Archives of Internal Medicine.* 2002;162(7):797-804.

physicians stated that they would consider both diet and drug therapy as the initial form of treatment to lower cholesterol levels, with less than one percent stating that they would consider lipid-lowering drug therapy as the initial therapy. Some of the physician barriers affecting the use of lipid-lowering therapy, included the fact that physicians do not adequately inform their patients about the use of these drugs and the lack of conviction in the benefits of lipid-lowering drugs.

The most important factor affecting the use of lipid-lowering drugs among patients as perceived by the physician was the cost of the medication followed by lack of understanding of the importance of lipid-lowering drugs.[297] Lai et al. conducted a chart review to study the cholesterol treatment in an HMO setting. A majority of the patients (65 percent, 224/348) needed either diet or drug therapy based on the NCEP-II guidelines. The authors stated that there exists poor adherence to guidelines among primary care physicians. [298] Based on a retrospective chart review of patients hospitalized in coronary care unit, a full lipid panel was ordered only 50 percent of the time. Assessment of CHD risk factors and treatment of hyperlipidemia by physicians was sub-optimal even for patients who were at a high risk for CHD.[299]

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[297] Yarzebski J, Bujor CF, Goldberg RJ, et al. A community-wide survey of physician practices and attitudes toward cholesterol management in patients with recent acute myocardial infarction. *Archives of Internal Medicine.* 2002;162(7):797-804.

[298] Lai L, Poblet M, Bello C. Are patients with hyperlipidemia being treated? Investigation of cholesterol treatment practices in an HMO primary care setting. *Southern Medical Journal.* 2000;93(3):283-286.

[299] Frolkis J, Zyzanski S, Schwartz J, et al. Physician noncompliance with the 1993 National Cholesterol Education Program, (NCEP-ATPII) guidelines. *Circulation.* 1998;98(9):851-855.

Gaw et al.[300] stated that in the primary care setting, physicians often fail to achieve the recommended LDL goals for their patients due to a number of factors including lack of adequate effectiveness of lipid-lowering drugs in reducing the LDL levels in frequently used doses.[301] Failure to achieve lipid goals are attributed to a large extent to inadequate doses of lipid-lowering agents. Most patients who begin treatment with statins remain at the initial dose.[302]

Danias and colleagues noted that less than 50 percent of hyperlipidemic patients in a Veterans Administration Medical Center were achieving the NCEP ATP II guidelines for cholesterol management mainly due to physicians' lack of adherence to guidelines. Of the total of 147 patients, only 94 (65%) had an additional cholesterol level measured during a 12 month follow-up. Only half the subjects who were eligible for cholesterol lowering drugs were receiving therapy and only one-third of patients who were on drugs attained desired LDL goals.[303]

Maviglia et al. showed that among secondary prevention patients only 31 percent were in compliance with the NCEP guidelines and 44 percent were on lipid-lowering therapy. Over half of the patients were not diagnosed or monitored for hyperlipidemia.

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[300] Gaw A. A new reality: achieving cholesterol-lowering goals in clinical practice. *Atherosclerosis Supplements.* 2002;2(4):5-8.

[301] Gaw A. A new reality: achieving cholesterol-lowering goals in clinical practice. *Atherosclerosis Supplements.* 2002;2(4):5-8.

[302] Andrews TC, Ballantyne CM, Hsia JA, et al. Achieving and maintaining National Cholesterol Education Program low-density lipoprotein cholesterol goals with five statins. *American Journal of Medicine.* 2001;111(3):185-191.

[303] Danias PG, O'Mahony S, Radford MJ, et al. Serum cholesterol levels are underevaluated and undertreated. *American Journal of Cardiology.* 1998;81(11):1353-1356.

Patient characteristics such as being male, white, having visited a cardiologist and having had a recent hospitalization for myocardial infarction, unstable angina or angina were significantly related to compliance to guidelines. The compliance rates did not differ with physician related characteristics such as age, gender, level of training, type and size of practice and volume of secondary prevention patients.[304]

Barriers to Physician Adherence to Guidelines

Barriers to physicians' adherence to guidelines include lack of awareness and familiarity to the guidelines. Even if physicians are aware of the guidelines they may lack the knowledge of the details of the guidelines. Lack of agreement to guidelines may also translate into physician non-adherence. Physicians' lack of self-efficacy in implementing preventive care guidelines in cardiology could decrease the likelihood of adhering to guidelines. Moreover, physicians' lack of confidence in achieving positive outcomes as a result of counseling patients on prevention due to patients' lack of compliance to physicians' recommendations also present a barrier to guideline implementation. Other barriers to adherence to guidelines include "clinical inertia" which is described as "the failure of health care providers to initiate or intensify therapy when indicated."[305] This is true especially for disorders such as hyperlipidemia which

[304] Maviglia SM, Teich JM, Fiskio J, et al. Using an electronic medical record to identify opportunities to improve compliance with cholesterol guidelines. *Journal of General Internal Medicine.* 2001;16(8):531-537.
[305] Cabana MD, Kim C. Physician adherence to preventive cardiology guidelines for women. *Women's Health Issues.* 2003;13(14):143-149.

does not manifest symptoms initially. Practice-related barriers include lack of time, reimbursement or reminder systems.[306,307]

In summary, lipid management in clinical practice is suboptimal mainly due to the lack of achievement of goals for LDL levels and lack of physician adherence to guidelines. Moreover, few patients who are eligible for drug therapy for the treatment of hyperlipidemia actually receive it. There has been no published study in the literature that has evaluated management of hyperlipidemia in the Medicaid population. Thus, this study aims to address that gap in literature. In addition, there have been few studies that have looked at lipid management in special populations including women and minority groups. Since the Medicaid data covers a large number of women and ethnic groups such as Hispanics and African Americans, this study aims to contribute to the understanding of lipid management in women and minorities.

Lipid Management in Special Populations

The following section provides an overview of lipid management in women, elderly and minority populations.

[306] Cabana MD, Kim C. Physician adherence to preventive cardiology guidelines for women. *Women's Health Issues.* 2003;13(14):143-149.
[307] Cabana MD, Rand CS, Powe NR, et al. Why don't physicians follow clinical practice guidelines: A framework for improvement. *Journal of the American Medical Association.* 1999;282(15):1458-1465.

Women

Cardiovascular diseases are the leading cause of death among women accounting for over half a million deaths annually. The "long-held belief" that heart disease is predominantly a male disease is a myth, as more women have died due to cardiovascular diseases than men since 1984. Based on results from the Framingham Heart Study, women have a three-fold greater chance of having a CHD event than developing breast cancer.[308]

The prevalence of CHD among white females, Mexican-American females and black females is 5.4 percent, 6.8 percent and 9.0 percent respectively.[309] The ATP III guidelines recommend a similar treatment approach for women as for men in both the primary and secondary prevention of CHD.[310] Recently published guidelines for the prevention of CVD in women calls for aggressive treatment based on the risk for CVD. The guidelines also strongly recommend lipid lowering therapy, preferably statins, for high-risk women.[311]

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[308] Kannel WB. The Framingham Study: historical insight on the impact of cardiovascular risk factors in men versus women. *Journal of Gender Specific Medicine.* 2002;5(2):27-37.

[309] American Heart Association. Heart Disease and Stroke Statistics - 2005 Update. *American Heart Association*. Available at: http://www.americanheart.org/presenter.jhtml?identifier=1928. Accessed January 15, 2005.

[310] Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *Journal of the American Medical Association.* 2001;285(19):2486-2497.

[311] Mosca L, Appel LJ, Benjamin EJ, et al. Evidence-based guidelines for cardiovascular disease prevention in women. *Circulation.* 2004;109(4):672-693.

Risk factors that predispose women to CHD include menopause that leads to a three-fold increase in the risk of CHD. A decrease in estrogen in postmenopausal women causes changes in lipid profiles, thus menopause accounts for an increased risk of CHD.[312] Cohort studies have established the association of hyperlipidemia with anincrease in CHD risk in women.[313] Increased levels of total cholesterol, LDL cholesterol and triglycerides have been observed in postmenopausal women.

The mean LDL-cholesterol levels are 24 percent higher (145 vs. 177 mg/dl) in women aged 55 to 64 years than those aged 35-44 years.[314] In addition, HDL cholesterol levels are a stronger predictor of CHD in women than in men.[315,316] For example in the Framingham Heart Study, a 1mg/dl increase in HDL cholesterol was associated with a three percent decrease in the incidence of CHD in women compared with two percent in men.[317] It is vital to recognize CHD risk factors in women at an early stage since two-thirds of sudden deaths occur in women with no CHD and they have a poorer prognosis

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[312] Kannel WB, Wilson PW. Risk factors that attentuate the female coronary disease advantage. *Archives of Internal Medicine.* 1995;155(1):57-61.
[313] Manolio TA, Pearson TA, Wenger NK, et al. Cholesterol and heart disease in older persons and women: review of an NHLBI workshop. *Annals of Epidemiology.* 1992;2(1-2):161-176.
[314] Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults. Summary of the Second Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *Journal of the American Medical Association.* 1993;269(23):3015-3023.
[315] Stevenson JC, Crook D, Godsland IF. Influence of age and menopause on serum lipids and lipoproteins in healthy women. *Atherosclerosis.* 1993;98(1):83-90.
[316] Matthews KA, Meilahn E, Kuller LH, et al. Menopause and risk factors for coronary heart disease. *New England Journal of Medicine.* 1989;321(10):641-646.
[317] Gordon DJ, Probstfield JL, Garrison RJ, et al. High-density lipoprotein cholesterol and cardiovascular disease: Four prospective American studies. *Circulation.* 1989;79(1):8-15.

and outcomes after CVD related procedures such as MI, PTCA and CABG compared to men. Moreover, women are more likely to die than men after a first MI.[318]

There exists a gender gap in treatment of hyperlipidemia.[319] Most studies have included only men or a small number of women, thus, data on lipid-lowering therapy in women are limited. In a review by Welty et al., the authors drew upon examples from the literature to show the existence of a gender gap in the treatment of hyperlipidemia. [320] For example, in a study of hospitalized CHD patients in the U.S. and Canada, the use of lipid-lowering therapy was greater in men than women.[321] In the HERS study, only 47 percent of the postmenopausal women with CHD were taking lipid-lowering drugs and 91 percent of the women had LDL levels above the NCEP goals.[322] Based on NHANES III, only 35 percent of women eligible for treatment were receiving treatment and only 42 percent of women with existing CHD were receiving lipid-lowering medications. [323]

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[318] Eaker ED, Chesebro JH, Sacks FM, et al. Cardiovascular disease in women. *Circulation.* 1993;88(4 pt 1):1999-1909.

[319] Welty F. Cardiovascular disease and dyslipidemia in women. *Archives of Internal Medicine.* 2001;161(4):514-522.

[320] Welty F. Cardiovascular disease and dyslipidemia in women. *Archives of Internal Medicine.* 2001;161(4):514-522.

[321] Miller M, Byington RP, Hunninghake D, et al. Lipid lowering therapy in CAD patients in academic medical centers: undertreatment and evidence of a gender gap. *Journal of the American College of Cardiology.* 1998;31(suppl):A186.

[322] Schrott H, Bittner V, Vittinghoff E, et al. Adherence to National Cholesterol Education Program treatment goals in postmenopausal women with heart disease: the Heart and Estrogen/Progestin Replacement study. *Journal of the American Medical Association.* 1997;277(16):1281-1286.

[323] Hoerger TJ, Bala MV, Bray JW, et al. Treatment patterns and distribution of low-density lipoprotein cholesterol levels in treatment-eligible United States adults. *American Journal of Cardiology.* 1998;82(1):61-65.

Some randomized clinical trials have established the beneficial effects of statins in the primary and secondary prevention of CHD in women. AFCAPS/TexCAPS was the first primary prevention trial to include women. Treatment with lovastatin was associated with a reduction of first acute major coronary event by 46 percent which was nine percent higher than that observed in men.[324] In the secondary prevention 4S study, simvastatin treatment reduced the risk of by 34 percent in both men and women.[325] LIPID study analyzed a subgroup of 1,516 women and found that "women benefited no differently than men," with regards to lipid-lowering treatment.[326] The WATCH trial studied the efficacy of atorvastatin in achieving ATP II LDL cholesterol targets in hyperlipidemic women with either confirmed CVD or risk factors for CVD. The authors concluded that atorvastatin was highly effective in achieving the ATP II target levels for LDL cholesterol in women with dyslipidemia and having CVD or risk factors for CVD.[327] In the more recent Heart Protection Study which included 5,082 women, a 24 percent reduction in major vascular events was observed in both sexes with simvastatin

[324] Downs JR, Clearfield M, S W, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels. Results of AFCAPS/TexCAPS. *Journal of the American Medical Association.* 1998;279(20):1615-1622.

[325] Kjekshus J, Berg K, Pedersen T, et al. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study (4S). *The Lancet.* 1994;344(8934):1383-1389.

[326] The LIPID Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *New England Journal of Medicine.* 1998;339(19):1349-1357.

[327] McPherson R, Angus C, Murray P, *et al.* Efficacy of atorvastatin in achieving National Cholesterol Education Program low-density lipoprotein targets in women with severe dyslipidemia and cardiovascular disease or risk factors for cardiovascular disease: The Women's Atorvastatin Trial on Cholesterol (WATCH). *American Heart Journal.* 2001;141(6):949-956.

treatment.[328] These studies provide support for the benefits of using cholesterol-lowering drugs in the prevention of CHD in women.

Elderly

There is limited evidence on the effect of statins in elderly patients aged 70 and older.[329,330] Studies have demonstrated the effectiveness of statins in both the primary and secondary prevention of CHD among the elderly.[331] Data suggest that hyperlipidemia plays a major role in the progression of CHD and is an independent risk factor of CHD in older adults.[332,333,334,335] The NHANES III demonstrated that 50 percent of patients above the age of 65 years qualify for dietary therapy and 10-25 percent for

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[328] The Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20536 high-risk individuals: A randomized placebo-controlled trial. *Lancet.* 2002;360(9326):7-22.

[329] Grundy SM, Cleeman JI, Rifkind BM, et al. Cholesterol lowering in the elderly population. *Archives of Internal Medicine.* 1999;159(15):1670-1678.

[330] LaRosa J, Jiang H, Vupputuri S. Effect of statins on risk of coronary disease: A meta-analysis of randomized controlled trials. *Journal of the American Medical Association.* 1999;124(282):2340-2346.

[331] Carlsson CM, Carnes M, McBride PE, et al. Managing dyslipidemia in older adults. *Journal of American Geriatric Society.* 1999;47(12):1458-1465.

[332] Harris T, Cooks EF, Kannel WB, et al. Proportional hazards analysis of risk factors for coronary heart disease in individuals aged 65 or older: The Framingham Heart Study. *Journal of the American Geriatric Society.* 1988;36(11):1023-1028.

[333] Corti MC, Guralnik K, Salive ME, et al. Clarifying the direct relation between total cholesterol levels and death from coronary heart disease in older persons. *Annals of Internal Medicine.* 1997;126(10):753-760.

[334] Rubin SM, Sidney S, Black D, et al. High blood cholesterol in elderly men and the excess risk for coronary heart disease. *Annals of Internal Medicine.* 1990;113(12):916-920.

[335] Benfante R, Reed D. Is elevated serum cholesterol levels a risk factor for coronary heart disease in the elderly? *Journal of the American Medical Association.* 1990;263(3):393-396.

drug therapy for hyperlipidemia.[336] In the 4S study, treatment with pravastatin was associated with 26 percent reduction in total cholesterol, 36 percent reduction in LDL cholesterol, 14 percent reduction in triglycerides and a seven percent increase in HDL cholesterol in elderly patients.[337] A meta-analysis conducted by LaRosa et al. showed that statin therapy was associated with a reduction in LDL levels and risk of major coronary events in patients aged 65 years or older (32 percent, 95% CI: 23-39%, $p<0.001$).[338] Aronow et al. studied the effect of statins on the incidence of new coronary events in older patients (ages ranged from 60 to 99 years) with peripheral arterial disease and LDL cholesterol levels $\geq$ 125 mg/dl. A total of 264 men and 396 women in a long-term care facility who were treated with either a statin or with no lipid-lowering agent, were followed prospectively.[339] The use of statin was significantly associated with the reduction in new coronary events in patients with ($p<0.0001$) (risk ratio 0.476, 95% CI:

[336] Sempos C, Cleeman JI, Carroll M, et al. Prevalence of high blood cholesterol among US adults: an update based on guidelines from the second report of the National Cholesterol Education Program Adult Treatment Panel. *Journal of the American Medical Association.* 1993;269(23):3009-3014.

[337] Miettinen TA, Pyorala K, Olsson AG, et al. Cholesterol-Lowering Therapy in Women and Elderly Patients With Myocardial Infarction or Angina Pectoris : Findings From the Scandinavian Simvastatin Survival Study (4S). *Circulation.* 1997;96(12):4211-4218.

[338] LaRosa J, Jiang H, Vupputuri S. Effect of statins on risk of coronary disease: A meta-analysis of randomized controlled trials. *Journal of the American Medical Association.* 1999;124(282):2340-2346.

[339] Aronow WS, Ahn C. Frequency of new coronary events in older persons with peripheral arterial disease and serum low-density lipoprotein cholesterol > or = 125 mg/dl treated with statins versus no lipid-lowering drug. *American Journal of Cardiology.* 2002;90(7):789-791.

0.367-0.617) and without ($p<0.0001$) (risk ratio 0.411, 95% CI: 0.288-0.586) prior myocardial infarction.[340]

Eaton et al. conducted a retrospective cohort study to determine the effect of statin use on one-year hospitalization and mortality rates for older patients in nursing homes.[341] The prevalence of statin use among patients with cardiovascular disease was 2.6 percent (1,313/51,559). The mortality rate at the end of one year was 31 percent lower for statin users compared to nonusers (hazard ratio=0.69, CI=0.58-0.81). Despite limited data on the effectiveness of cholesterol-lowering therapy in women and elderly, research supports the use of cholesterol-lowering therapy in the prevention of CHD in women and the elderly.

Minorities

Cardiovascular diseases are the leading cause of death among Hispanics and African Americans. There has been a lack of sufficient studies of CHD in minorities.[342] Minority populations have a higher relative risk for death related to stroke as compared to

[340] Aronow WS, Ahn C. Frequency of new coronary events in older persons with peripheral arterial disease and serum low-density lipoprotein cholesterol > or = 125 mg/dl treated with statins versus no lipid-lowering drug. *American Journal of Cardiology.* 2002;90(7):789-791.

[341] Eaton C, Lapane K, Murphy J, et al. Effect of statin (HMG-CoA reductase inhibitor) use on 1-year mortality and hospitalization rates in older patients with cardiovascular disease living in nursing homes. *Journal of American Geriatric Society.* 2002;50(8):1389-1395.

[342] Harris-Hooker S, Sanford GL. Lipids, lipoproteins and coronary heart disease in minority populations. *Atherosclerosis.* 1994;108(suppl):S83-S104.

the non-Hispanic white population.[343] Among Mexican Americans aged 20 years and older the prevalence of CHD is 7.2 percent in men and 6.8 percent in women. The prevalence of CHD among non-Hispanic blacks 20 years and older is 7.1 percent and 9.0 percent in men and women respectively. The prevalence of CHD among whites is, 6.9 percent among males and 5.4 percent among females.[344]

A cross-sectional survey of 417 Mexican cities revealed a high prevalence of low HDL concentrations and mixed hyperlipidemia among the Mexican population. Over twelve percent of the subjects had simultaneous elevation of cholesterol and triglyceride concentrations.[345] Hispanics with diabetes have a higher risk of hyperlipidemia than those without.[346] Thus, it is important to understand the risk factors and the management of hyperlipidemia among the minority populations. In the Corpus Christi Heart Project, Mexican Americans had greater hospitalization rates due to myocardial infarction than

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[343] American Heart Association. Heart Disease and Stroke Statistics - 2005 Update. *American Heart Association*. Available at: http://www.americanheart.org/presenter.jhtml?identifier=1928. Accessed January 15, 2005.

[344] American Heart Association. Heart Disease and Stroke Statistics - 2005 Update. *American Heart Association*. Available at: http://www.americanheart.org/presenter.jhtml?identifier=1928. Accessed January 15, 2005.

[345] Aguilar-Salinas CA, Olaiz G, Valles V, et al. High prevalence of low HDL cholesterol concentrations and mixed hyperlipidemia in a Mexican nationwide survey. *Journal of Lipid Research.* 2001;42(8):1298-1307.

[346] Bermudez OI, Velez-Carrasco W, Schaefer EJ, et al. Dietary and plasma lipid, lipoprotein, and apolipoprotein profiles among elderly Hispanics and non-Hispanics and their association with diabetes. *Am J Clin Nutr.* 2002;76(6):1214-1221.

non-Hispanic whites (age-adjusted rate ratios=1.59 95% CI: 1.05-2.41 for women and 1.31; 95% CI: 1.18-1.45 for men).[347]

There exist disparities in cholesterol management among the minority population. Data from the NHANES III showed that African Americans and Mexican Americans were significantly less likely than whites to have ever had their blood cholesterol checked (OR=0.7 for both groups, $p<0.001$) and they were less likely than whites to take cholesterol lowering medications ($p=0.05$).[348] Non-whites were more likely to receive counseling for cholesterol management than whites (1.7% vs. 1.0%, $p<0.001$); however, they were slightly less likely to be screened for cholesterol than whites (2.5% vs. 2.9%, $p=0.034$).[349] Adherence to statin therapy among African-Americans was lower as compared to whites (59.9% vs. 74.1%, $p<0.001$).[350] African Americans were less likely than whites to achieve the NCEP-II goals for LDL-C (40.9% vs. 56.9%, $p<0.001$).[351]

In summary, cholesterol management among the minority population remains suboptimal. Very few studies have addressed the management of hyperlipidemia and

[347] Goff DC, Nichaman MZ, Chan W, et al. Greater incidence of hospitalized myocardial infarction among Mexican Americans than Non-Hispanic Whites : The Corpus Christi Heart Project, 1988-1992. *Circulation.* 1997;85(6):1433-1440.
[348] Nelson K, Norris K, Mangione CM. Disparities in the diagnosis and pharmacologic treatment of high serum cholesterol by race and ethnicity: data from the Third National Health and Nutrition Examination Survey. *Archives of Internal Medicine.* 2002;162(8):929-935.
[349] Stafford RS, Blumenthal D, Pasternak R. Variations in cholesterol management practices of U.S physicians. *Journal of the American College of Cardiology.* 1997;29(1):139-146.
[350] Charles H, Good CB, Hanusa B, et al. Racial differences in adherence to cardiac medications. *Journal of National Medical Association.* 2003;95(1):17-27.
[351] Williams ML, Morris M, Ahmad U, et al. Racial differences in compliance with NCEP-II recommendations for secondary prevention at a Veterans Affairs medical center. *Ethnicity & Disease.* 2002;12(1):58-62.

CHD in the minority populations. The current research utilizes the Texas Medicaid database that includes a large proportion of minority population thus presenting the opportunity to further study the management of hyperlipidemia.

SECTION V

IMPACT OF PHYSICIAN SPECIALTY ON THE MANAGEMENT OF HYERLIPIDEMIA AND CHD

Impact of Physician Specialty

In the U.S. health care system, primary care physicians act as "gatekeepers" to reduce healthcare costs. Access to specialists such as cardiologists in managed care organizations could be restricted due to the belief that specialists are costlier than generalists. There is a need for more data to understand the differences in cost and quality of care provided by specialists versus generalists.[352] A few studies have evaluated the differences in management and outcomes of hyperlipidemic patients with respect to physician specialty.

Whyte et al. found that management of hyperlipidemia in secondary prevention patients varied by physician specialty (general practitioners or cardiologists).[353] Patients visiting cardiologists were twice as likely to receive drug therapy for LDL levels >130 mg/dl. However, there was no difference in the type of cholesterol lowering medication prescribed by the two specialties.

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[352] Nash IS, Nash DB, Fuster V. Do cardiologists do it better? *Journal of the American College of Cardiology*. 1997;29(3):475-478.

[353] Whyte JJ, Filly AL, Jollis JG. Treatment of hyperlipidemia by specialists versus generalists as secondary prevention of coronary artery disease. *American Journal of Cardiology*. 1997;80(10):1345-1347.

Strafford et al. showed that physician specialty also affected cholesterol screening practices.[354] The rate of screening among patients without known hyperlipidemia was higher among cardiologists (5.5%), and other internists (6.1%), compared to family physicians and general practitioners (3.3%) and other physicians (1.5%) ($p < 0.001$). Internists (38.7%), cardiologists (35.3%), family physicians and general practitioners (36.4%) were more likely to counsel patients with hyperlipidemia than other physicians (16.2%, $p < 0.001$). Patients visiting cardiologists were five times more likely to be counseled about cholesterol management compared to those visiting other physicians. Cardiologists (37.7%) and internists (28.5%) were more likely to prescribe lipid-lowering medications than general practitioners and family physicians (17.6%) and other physicians (15%) ($p < 0.001$).[355] A cross-sectional mail survey of generalists and cardiologists which included primary prevention case simulations revealed that general physicians and family physicians overestimated the baseline cardiovascular risk and benefit of therapy as compared with cardiologists.[356]

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[354] Stafford RS, Blumenthal D, Pasternak R. Variations in cholesterol management practices of U.S physicians. *Journal of the American College of Cardiology.* 1997;29(1):139-146.

[355] Stafford RS, Blumenthal D, Pasternak R. Variations in cholesterol management practices of U.S physicians. *Journal of the American College of Cardiology.* 1997;29(1):139-146.

[356] Friedmann PD, Brett AS, Mayo-Smith MF. Differences in generalists' and cardiologists' perceptions of cardiovascular risk and the outcomes of preventive therapy in cardiovascular disease. *Annals of Internal Medicine.* 1996;124(4):414-421.

Patients treated by cardiologists were more likely to receive aspirin, heparin or beta-adrenergic blocking agents than those treated by internists. Similarly, cardiologists were more likely to treat patients with aspirin and thrombolytic agents than general physicians.[357] Cardiovascular-related procedures such as coronary revascularization, coronary angioplasty and heart catheterization were more likely to be performed in patients treated by cardiologists versus internists.[358] Cardiologists used coronary angiography more frequently compared to general physicians.[359] Similar results were observed among Medicare patients with acute MI, with cardiologists using a high rate of cardiac procedures as well as medications such as aspirin, beta-blockers and thrombolytic agents. Patients admitted to the hospital by a cardiologist were 12 percent less likely to die within a year than those admitted by a primary care physician.[360]

[357] Ayanian JZ, Guadagnoli E, McNeil BJ, et al. Treatment and outcomes of acute myocardial infarction among patients of cardiologists and generalist physicians. *Archives of Internal Medicine.* 1997;157(22):2570-2576.
[358] Schreiber TL, Elkhatib A, Grines CL, et al. Cardiologist versus internist management of patients with unstable angina: Treatment patterns and outcomes. *Journal of the American College of Cardiology.* 1995;26(3):577-582.
[359] Ayanian JZ, Guadagnoli E, McNeil BJ, et al. Treatment and outcomes of acute myocardial infarction among patients of cardiologists and generalist physicians. *Archives of Internal Medicine.* 1997;157(22):2570-2576.
[360] Jollis JG, Delong ER, Peterson ED, et al. Outcome of acute myocardial infarction according to the specialty of the admitting physician. *New England Journal of Medicine.* 1996;335(25):1880-1887.

Summary

The above studies show that there is a disparity in management of cholesterol and CHD between physician specialties. Cardiologists use more resources such as cardiovascular procedures and lipid-lowering therapy than general physicians. Some studies have also indicated better outcomes associated with treatment with cardiologists. These findings could be attributed to additional training and experience in treating patients with CHD and associated risk factors.

SECTION VI

PHARMACOECONOMIC EVALUATIONS OF LIPID-LOWERING THERAPY

CHD accounts for huge expenditures of healthcare resources. Lipid-lowering therapy, primarily statins, have proved to be effective in lowering CHD mortality and morbidity in both primary and secondary prevention trials. Despite the proven benefits of statin therapy, if all patients with hyperlipidemia were treated with statins, the cost of treatment would exceed billions of dollars. Pharmacoeconomic evaluations such as cost-effectiveness analyses help in providing a framework for the effective allocation of limited healthcare resources.[361] The most commonly used pharmacoeconomic evaluation used in cardiovascular disease intervention is a form of cost-effectiveness analysis called cost per year of life saved. For any lipid-lowering medication, a ratio of ≤$50,000 per year of life saved is considered to be cost-effective since it is comparable with other interventions such as chronic hemodialysis, breast cancer screening or coronary artery bypass graft surgery.[362] The cost-effectiveness of lipid-lowering therapy varies with respect to its use in primary or secondary prevention of CHD.

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[361] Jacobson TA. Maximizing the cost-effectiveness of lipid-lowering therapy. *Archives of Internal Medicine.* 1998;158(18):1977.

[362] Hay JW, Yu WM, Ashraf T. Pharmacoeconomics of lipid-lowering agents for primary and secondary prevention of coronary artery disease. *Pharmacoeconomics.* 1999;15(1):47-74.

Primary Prevention

Primary prevention statin trials such as the WOSCOPS and AFCAPS/TexCAPS have shown significant reduction in risk of CHD. The WOSCOPS study has been used as a model for determining the benefit of statin therapy in primary prevention. Cato et al. used data from the WOSCOPS study to assess the efficiency of pravastatin in preventing a cardiovascular event in men with hypercholesterolemia. The results showed that if 10,000 men were treated with pravastatin, 318 would not make a transition from health to cardiovascular disease (number needed to treat would be 31.4). This would translate to a net discounted cost of £2 million over five years and an undiscounted gain of 2460 years of life amounting to £8,121 per year of life gained or £20,375 per year of life gained if benefits were discounted. When the analysis included only the top 40 percent of high-risk men, there was a reduction in the number needed to treat to prevent one cardiovascular event to 22.5 (£5601 per life year gained (undiscounted) and £13995 per life year gained (discounted). The study implied that use of pravastatin in primary prevention is cost-beneficial in patients with hyperlipidemia.

Badia and colleagues compared the economics of treatment with simvastatin and atorvastatin in reducing LDL levels in primary prevention patients in ten European countries.[363] Data for the analysis were obtained from a one-year, double-blind, parallel-

[363] Badia X, Russo P, Attanasio E. A comparative economic analysis of simvastatin versus atorvastatin: Results of the Surrogate Marker Cost-Efficacy (SMaC) study. *Clinical Therapeutics.* 1999;21(10):1788-1796.

group clinical trial. Patients were randomized to receive atorvastatin 20 mg/day or simvastatin 20 mg/day. There was no significant difference in the percentage of patients achieving the LDL goals between the two groups. However, the total cost of treatment was lower in the simvastatin group than in the atorvastatin group (euros 429 vs. 538, $p<0.0001$). In eight out of the ten countries, the cost of treatment was lower for simvastatin than atorvastatin, and in the remaining two countries there were no cost differences. Only drug costs were used in the study due to lack of availability of data on the rates of hospitalization and procedures in the atorvastatin group.

Hilleman et al. conducted a pharmacoeconomic evaluation of statins based on the CURVES study. The CURVES study was a multicenter, open-label trial that compared the efficacy of five statins (atorvastatin, fluvastatin, lovastatin, pravastatin and simvastatin). A total of 534 patients were randomized to 15 different treatment groups over a period of eight weeks. The results of the CURVES study showed that atorvastatin 10, 20 and 40 mg/day were significantly associated with reduction in LDL cholesterol levels as compared to other statins. Hilleman et al., calculated cost-effectiveness expressed as annual acquisition cost per percentage LDL reductions. The results showed that atorvastatin 10 mg/day ($17.96) was the most cost-effective, followed by fluvastatin 40 mg/day ($19.83), atorvastatin 20 mg/day ($22.85), and atorvastatin 40 mg/day ($24.96).[364]

[364] Hillemann DE, Heineman SM, Foral PA. Pharmacoeconomic assessment of HMG-CoA reductase inhibitor therapy: An analysis based on the CURVES study. *Pharmacotherapy*. 2000;20(7):819-822.

Spearman et al. evaluated the cost-effectiveness of statins for initial therapy in a primary care setting of a managed care organization.[365] Effectiveness was defined as the percent reduction in LDL levels based on six months of initial therapy. Both direct and indirect costs were included in the analyses. Indirect costs included time lost due to physician visits or laboratory testing, transit time and work days missed due to adverse events. The number of patients who remained on the same drug with no dose changes were highest in those receiving fluvastatin (72 percent), followed by simvastatin (71 percent), pravastatin (48 percent), lovastatin (43 percent) ($p=0.001$). The cost-effectiveness ratio for fluvastatin was lower than the other statins ($p<0.01$). Drug compliance that was measured in terms of possession ratio was highest for fluvastatin and simvastatin and lowest for lovastatin.

Hamilton et al. evaluated the lifetime cost-effectiveness of lovastatin 20mg/day in preventing CHD in patients with hyperlipidemia.[366] This study took into account the benefits of lowering total cholesterol and increasing HDL cholesterol. The authors used a computer model to estimate the benefits of risk factors modification. The results of the analysis showed that an increase in HDL cholesterol lowered the cost-effectiveness ratio by 40 percent. The cost-effectiveness ratio ranged from $20,882 for men aged 50 years

[365] Spearman M, Summers K, Moore V, et al. Cost-effectiveness of initial therapy with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors to treat hypercholesterolemia in a primary care setting of a managed-care organization. *Clinical Therapeutics.* 1997;19(3):582-602.

[366] Vivian HH, Francois-Eric R, Hanna Z, et al. The cost-effectiveness of HMG-CoA reductase inhibitors to prevent coronary heart disease: estimating the benefits of increasing HDL-C. *Journal of the American Medical Association.* 1995;273(13):1032-1038.

to $36,627 for women aged 60 years with additional risk factors. The ratio increased by 23 percent for elderly patients aged 70 years due to non-CHD costs resulting from longer life expectancy. Indirect costs and direct costs related to side effects were not considered in the analysis.[367]

Martens and Guibert calculated the cost-effectiveness of different statins available in Canada for the primary prevention of CHD.[368] Risk functions from the Framingham Heart Study were used in the model. The cost-effectiveness ratio varied from $56,200/year of life saved for pravastatin 20 mg to $38,800/year of life saved for fluvastatin 40 mg. The results showed that treatment with fluvastatin was most cost-effective as compared to pravastatin, lovastatin and simvastatin in the primary prevention of CHD. The cost-effectiveness ratio varied with the pretreatment risk factors such as cholesterol levels and presence of additional risk factors.[369]

Huse et al. studied the cost-effectiveness of five statins: atorvastatin (10 mg), fluvastatin (20 mg), lovastatin (20 mg), pravastatin (20 mg), simvastatin (10 mg) in the primary and secondary prevention of CHD.[370] The model evaluated the cost-

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[367] Vivian HH, Francois-Eric R, Hanna Z, et al. The cost-effectiveness of HMG-CoA reductase inhibitors to prevent coronary heart disease: estimating the benefits of increasing HDL-C. *Journal of the American Medical Association.* 1995;273(13):1032-1038.

[368] Martens LL, Guibert R. Cost-effectiveness analysis of lipid-modifying therapy in Canada: Comparison of HMG-CoA reductase inhibitors in the primary prevention of coronary heart disease. *Clinical Therapeutics.* 1994;16(6):1052-1062.

[369] Martens LL, Guibert R. Cost-effectiveness analysis of lipid-modifying therapy in Canada: Comparison of HMG-CoA reductase inhibitors in the primary prevention of coronary heart disease. *Clinical Therapeutics.* 1994;16(6):1052-1062.

[370] Huse DM, Russell MW, Miller GE, et al. Cost-effectiveness of statins. *American Journal of Cardiology.* 1998;82(11):1357-1363.

effectiveness of statins across gender, the presence or absence of three risk factors, across three age groups (45, 55 and 65 years) and across two LDL levels (190 mg/dl and 220 mg/dl). Effects of statins on serum lipids were obtained from data on the product labels. Framingham Heart Study coronary risk equations were developed to estimate the annual risks of coronary event occurrences. Outcome measures included net cost as calculated by the difference in the cost of statin therapy and the savings in CHD treatment, gain in life expectancy and cost per-life saved. Atorvastatin was more cost-effective than the other statins in both primary and secondary prevention of CHD. For example, in a 55 year old male primary prevention patient with LDL levels of 220 mg/dl and no other risk factors, the cost-effectiveness ratio (incremental cost/year of life saved) for atorvastatin was $32,609, followed by simvastatin $39,247, fluvastatin $42,738, pravastatin $47,077 and lovastatin 59,036. The cost-effectiveness ratio for statin therapy was favorable for secondary prevention in both men and women with multiple risk factors. For primary prevention, the cost-effectiveness ratio was favorable for men with risk factors and women with "highest risk" profiles. Overall, secondary prevention was more cost-effective than primary prevention.[371]

[371] Huse DM, Russell MW, Miller GE, et al. Cost-effectiveness of statins. *American Journal of Cardiology*. 1998;82(11):1357-1363.

Cost-effectiveness ratios based on different patient characteristics for primary and secondary prevention of CHD were calculated.[372] Men and women between the ages of 35 to 84 years of age were divided into subgroups based on age, sex, and the presence or absence of four CHD risk factors. The authors used the Coronary Heart Disease Policy Model to evaluate the effects and costs of cholesterol lowering therapy in each risk groups. Results from five studies were pooled to estimate the effects of a low-cholesterol diet. Data to estimate the effectiveness of primary prevention with a statin were obtained from three long-term studies of pravastatin. Estimates for effectiveness of statins in secondary prevention were obtained from the results of the Scandinavian Simvastatin Survival Study. The cost-effectiveness for primary prevention ranged from $54,000 to $420,000 per QALY controlling for individual risk factors. Cost-effectiveness ratio for the secondary prevention with a statin was less than $50,000 per QALY across all patient subgroups and risk categories. Overall, the secondary prevention was more cost-effective than primary prevention. The ratios were more favorable for higher risk factors (especially for blood pressure and HDL levels), increasing age and for male gender. [373]

[372] Prosser LA, Stinnett AA, Goldman PA, et al. Cost-effectiveness of cholesterol-lowering therapies according to selected patient characteristics. *Annals of Internal Medicine*. 2000;132(10):769-779.

[373] Prosser LA, Stinnett AA, Goldman PA, et al. Cost-effectiveness of cholesterol-lowering therapies according to selected patient characteristics. *Annals of Internal Medicine*. 2000;132(10):769-779.

Russell et al. evaluated the cost-effectiveness of statins versus no drug therapy in primary and secondary prevention of CHD disease in Canada using a Markov model.[374] Risk factors were estimated using the Canadian population survey data and coronary risk was estimated using the coronary risk equations from the Framingham Heart Study. Results of the analyses showed that the cost per year of life gained was lowest for atorvastatin and highest for pravastatin across all risk profiles. For example, for patients 55 years of age and LDL levels of 160 mg/dl, the incremental cost per year of life saved was Can$ 64,419 for atorvastatin, Can$ 83,226 for lovastatin, Can$ 87,906 for simvastatin, Can$ 88,077 for fluvastatin and Can$ 109,034 for pravastatin.[375]

Russell et al.[376] calculated the direct medical costs (pharmacy, professional, hospital, and home health) related to the treatment of CHD in the U.S. using a Markov model. The medical cost (in 1995 dollars) for the first year of treatment of CHD was estimated to be $17,532 for fatal acute myocardial infarction, $15,540 for non-fatal AMI, $2,569 for stable angina, $12,058 for unstable angina and $713 for sudden CHD death. Based on the annual incidence of 616,900 cases of CHD in the U.S., the first-year treatment cost totaled $5.54 billion. Five and ten year projected total direct medical costs in 1995 dollars for patients with CHD were estimated to be $71.5 billion and $126.6

[374] Russell MW, Huse DM, Miller JD, et al. Cost-effectiveness of HMG-CoA reductase inhibition in Canada. *Canadian Journal of Clinical Pharmacology.* 2001;8(1):9-16.
[375] Russell MW, Huse DM, Miller JD, et al. Cost-effectiveness of HMG-CoA reductase inhibition in Canada. *Canadian Journal of Clinical Pharmacology.* 2001;8(1):9-16.
[376] Russell MW, Huse DM, Drowns S, et al. Direct Medical Costs of Coronary Artery Disease in the United States. *American Journal of Cardiology.* 1998;81(9):1110-1115.

billion, respectively. For patients initially free of CHD the cumulative direct costs for five and ten years were estimated to be $9.2 billion and $16.5 billion respectively.

Koren et al. conducted a 54-week, randomized controlled trial to assess the total cost associated with reaching NCEP goals with different statins (atorvastatin, simvastatin, lovastatin and fluvastatin).[377] The mean total cost of care to reach NCEP goals was lower for atorvastatin ($1064) compared with simvastatin ($1471), lovastatin ($1972), and fluvastatin ($1542). Patients treated with atorvastatin were more likely to reach NCEP goals ($p<0.05$), required fewer office visits ($p<0.001$) and less likely to be on combination therapy with colestipol ($p=0.001$) than other statins.

Secondary Prevention

A number of studies have evaluated the cost-effectiveness of lipid-lowering therapy in the secondary prevention of CHD. Elliott et al. compared the cost effectiveness of six statins (atorvastatin, fluvastatin, lovastatin, pravastatin or simvastatin) in the secondary prevention of acute myocardial infarction in patients between 60 and 85 years of age.[378] A Markov model was used to project the number of survivors and the

[377] Koren M, Smith DG, Hunninghake D, et al. The cost of reaching National Cholesterol Education Program (NCEP) goals in hypercholesterolaemic patients. A comparison of atorvastatin, simvastatin, lovastatin and fluvastatin. *Pharmacoeconomics.* 1998;14(1):59-70.

[378] Elliott WJ, Weir DR. Comparative cost-effectiveness of HMG-CoA reductase inhibitors in secondary prevention of acute myocardial infarction. *American Journal of Health System Pharmacy.* 1999;56(17):1726-1732.

annual direct and indirect cost per survivor associated with the reduction in non-fatal MI recurrences. Doses and costs of statins necessary to reduce the LDL cholesterol by 36 percent were considered for the analysis. Transition probabilities for the Markov model were obtained from the 4S trial. Lovastatin had the highest cost per life saved (YOLS) ($15,073) whereas atorvastatin had the lowest cost/YOLS ($5,421). The cost/YOLS for simvastatin was $9,232, for pravastatin $8,575, for cerivastatin $6,158 and for fluvastatin $5,790. The cost-effectiveness of statin therapy was impacted by the patient's age with higher cost-effectiveness per year of life saved for older than younger patients.

Maclaine and Patel conducted a cost-effectiveness analysis of five statins to achieve target LDL levels in secondary prevention patients based on an economic model. Efficacy estimates of each statin were derived from meta-analysis.[379] The model estimated the proportion of patients achieving target LDL levels under different scenarios. The incremental cost per patient treated to target LDL levels compared to no treatment was lowest for atorvastatin (£383), followed by simvastatin (£431), cerivastatin (£501), fluvastatin (£820) and pravastatin (£1213). Overall, the cost-effectiveness ratios were lowest for atorvastatin. Under a fixed drug budget, more patients could be treated effectively with atorvastatin compared to other statins.[380]

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[379] Maclaine GD, Patel H. A cost-effectiveness model of alternative statins to achieve target LDL-cholesterol levels. *International Journal of Clinical Practice.* 2001;55(4):243-249.

[380] Maclaine GD, Patel H. A cost-effectiveness model of alternative statins to achieve target LDL-cholesterol levels. *International Journal of Clinical Practice.* 2001;55(4):243-249.

Grover et al. studied the long-term benefits and cost-effectiveness of lipid modification in secondary prevention patients based on data from the Lipid Research Clinics cohort.[381] Among low-risk individuals, long-term benefit of lipid modification ranged from $5424 to $9548 per year of life saved for men and $8389 to $13,747 per year of life saved for women. Among high risk patients, the cost ranged from $4487 to $8532 per year of life saved for men and $5138 to $8398 per year of life saved for women.

Ashraf and associates evaluated the cost-effectiveness of pravastatin in the secondary prevention of CHD using data from two plaque regression trials.[382] Mortality data were estimated from the Framingham Heart Study. Life-years saved for a 10 year time period were calculated with the help of a Markov model. Cost per year of life saved in men with CHD decreased with the increase in the number of risk factors. The ratios were $9632 (for one risk factor) $7156 (for two risk factors) and $5473 (for more than or equal to three risk factors). Due to lack of data indirect costs were not included in the model.[383]

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[381] Grover SA, Coupal L, Paquet S, et al. Cost-effectiveness of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors in the secondary prevention of cardiovascular disease. *Archives of Internal Medicine.* 1999;159(6):593-600.

[382] Ashraf T, Hay JW, Pitt B, et al. Cost-effectiveness of pravastatin in the secondary prevention of coronary artery disease. *American Journal of Cardiology.* 1996;78(4):409-414.

[383] Ashraf T, Hay JW, Pitt B, et al. Cost-effectiveness of pravastatin in the secondary prevention of coronary artery disease. *American Journal of Cardiology.* 1996;78(4):409-414.

Summary

Based on a review of the literature, treatment for secondary prevention is more cost-effective than primary prevention. This could be due to the fact that individuals for secondary prevention are at a higher risk for recurrent coronary events than primary prevention patients; thus, there would be increased cost savings from events avoided at similar treatment costs. Cost-effectiveness ratios are sensitive to baseline cholesterol levels and risk factors with higher ratios associated with greater number of risk factors and higher cholesterol levels.

SECTION VII

ADVANTAGES AND DISADVANTAGES OF THE USE OF CLAIMS DATABASES IN HEALTH OUTCOMES RESEARCH

The proposed study uses the Texas Medicaid prescriptions claims and healthcare services utilization claims database. A brief discussion of the advantages and disadvantages for the use of claims databases follows.[384]

Advantages

The major advantage of using a medical claims database is its scope to link pharmacy claims and other health care resource utilization databases allowing for the examination of the relationships between different aspects of healthcare use. Claims databases allow the evaluation of treatments in real life situations. Patient information and patient care information are available for long periods of time, thus enabling the use of databases for longitudinal studies. Because databases are large, they can be used for epidemiological research including studying patients with rare diseases and specific subpopulations. Any changes in study designs can be easily implemented in research involving the use of database. Research using databases is less costly and less time consuming compared to collecting primary data such as those in clinical trials.

[384] Motheral BR, Fairman KA. The use of claims databases for outcomes research: rationale, challenges, and strategies. *Clinical Therapeutics.* 1997;19(2):346-366.

Moreover, the large number of cases in a claims database offers statistical power at lower costs compared to clinical trials.

Disadvantages

Despite the number of advantages for use in outcomes research, claims databases do pose threats to internal, external and construct validity.[385] Moreover, administrative databases are collected for the purpose of verifying and paying claims; thus, they contain a minimum set of information to carry out that purpose rather than include information for research purposes.[386] Motheral and Fairman enumerates the following examples of threats to internal validity imposed by claims database research.[387]

1) Diagnostic information such as the use of the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) in database research may not always be reliable or valid. Under-coding and over-coding of diagnoses can occur that could result in a study bias. Over-coding can occur either intentionally or unintentionally as a result of economic incentives related to diagnostic-related groups. Under-coding might occur as the physician might not record secondary diagnoses due to limitations in the number of diagnoses that can be recorded in the insurance claims forms.

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[385] Motheral BR, Fairman KA. The use of claims databases for outcomes research: rationale, challenges, and strategies. *Clinical Therapeutics.* 1997;19(2):346-366.
[386] Iezzoni LI. Assessing quality using administrative data. *Annals of Internal Medicine.* 1997;127(8 pt 2):666-674.
[387] Motheral BR, Fairman KA. The use of claims databases for outcomes research: rationale, challenges, and strategies. *Clinical Therapeutics.* 1997;19(2):346-366.

2) Differences in compliance between various therapeutic categories need to be taken into account before concluding about relationships between treatment and outcome variables.

3) Misclassification of exposure could lead to bias in the study results. Moreover, the results could also be affected by the possibility of referral bias and protopathic bias.

4) Another potential threat to internal validity includes the presence of confounding variables. Severity of illness is frequently cited as a confounder in outcomes research. Inadequate clinical information present in databases limits the adjustments for severity.[388] Important confounding variables such as smoking status, family history of illness, alcohol use, drug use and use of over-the-counter-drugs are missing from the Medicaid database hence they cannot be controlled for in the study.[389]

Construct validity refers to the degree to which a variable measures what it is meant to measure. In the database, the use of a drug as a proxy for the presence of a medical condition can be misleading. Some drugs have multiple uses and thus, it may be difficult to determine the disease state. Also, the use of drugs for off-label purposes could lead to the risk of misidentifying patients to a medical condition that they might not

[388] Motheral BR, Fairman KA. The use of claims databases for outcomes research: rationale, challenges, and strategies. *Clinical Therapeutics*. 1997;19(2):346-366.
[389] Carson J, Wayne R, Strom B. Medicaid Databases. In: Strom B, ed. *Pharmacoepidemiology*. New York: John Wiley & Sons, Ltd.; 2000:307-324.

have. Similarly, patients with the medical condition of interest might not be included since not all diagnosed individuals receive treatment.

External validity refers to the degree of generalizability of the study. For example, a study conducted using a Medicaid database would not be generalizable to a large population since the characteristics of the Medicaid population include low income and disabled individuals who might have different patterns of health care utilization as compared to the rest of the population. Similarly, plan design, geographic variations and differences in cost across time and place limit the generalizability of the study. With increasing use of healthcare databases in research, the right to safeguard patient privacy and confidentiality has become an important issue. Unauthorized persons or agencies might get access to health care information which could be sold to marketing firms.[390]

In addition to the above limitations, eligibility changes to the insurance program such as Medicaid may cause patients to be terminated from the study. Thus, it could lead to misinterpretation that the outcome of interest did not occur in the patient when in reality, the patient was no longer part of the database. This limitation can be addressed using the eligibility files to ensure that the patient is enrolled in the database.[391] Medical claims for individuals above 65 years of age may be incomplete due to dual eligibility in Medicaid and Medicare programs. Missing data such as those for prescription claims could be problematic especially when assessing prescription refill patterns since failure to

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[390] Gostin L. Health care information and the protection of personal privacy: Ethical and legal considerations. *Annals of Internal Medicine.* 1997;127(8 pt 2):683-690.
[391] Carson J, Wayne R, Strom B. Medicaid Databases. In: Strom B, ed. *Pharmacoepidemiology*. New York: John Wiley & Sons, Ltd.; 2000:307-324.

refill prescriptions could be a result of missing claims rather than lack of patient adherence.[392] Despite the disadvantages of the use of databases, they are an important resource in outcomes research. Nevertheless, the limitations of database research need to be acknowledged.

[392] Hennessy S, Bilker W, Weber A, et al. Descriptive analyses of the integrity of a US Medicaid claims database. *Pharmacoepidemiology and Drug Safety.* 2003;12(2):103-111.

SECTION VIII

TEXAS MEDICAID DATABASE AND CARDIOVASCULAR DISEASE IN TEXAS

Texas Medicaid Program

The Medicaid program in Texas, established in 1967, is a jointly funded state-federal program administered by the Texas Health and Human Services Commission. As of February 2004, 2.5 million Texans were enrolled in the Medicaid program.[393] For the year fiscal year 2004, Medicaid expenditures were projected to be $15.5 billion.[394] The categories of individuals eligible for Medicaid include low income families and children including pregnant women, recipients of Temporary Assistance to Needy Families (TANF) or Supplemental Security Income (SSI) and the aged and disabled. Females (56%) and non disabled children (59%) make up the largest share of the Texas Medicaid program. Hispanics constitute the largest portion of Medicaid recipients (51%) followed by Caucasians (26%) and African Americans (19%).[395] Medicaid covers basic health care including physician services, outpatient and inpatient services, pharmacy, laboratory and x-ray services. Long-term care facilities, nursing facilities, and intermediate care

[393] Texas Health and Human Services Commission. Texas Medicaid In Perspective. *Texas Medicaid in Perspective*. Austin; 2004:1-1-1-4.
[394] Texas Health and Human Services Commission. Texas Medicaid In Perspective. *Texas Medicaid in Perspective*. Austin; 2004:1-1-1-4.
[395] Texas Health and Human Services Commission. Clients and Benefits. *Texas Medicaid in Perspective*. Austin; 2004:4-1-4-24.

facilities for persons with mental retardation as well as hospice care are also funded by Medicaid. Medicaid also provides coverage for prescription drugs through the Texas Medicaid Vendor Drug Program.

Texas Medicaid Vendor Drug Program

The Texas Medicaid program offers coverage for prescription drug services to its enrollees. This program is administered by the Texas Medicaid Vendor Drug Program (VDP). The VDP covers up to three outpatient prescriptions per month per adult recipient. Medicaid clients who are in an inpatient hospital, long-term care residents, managed care recipients and children under 21 years are not subject to the three prescription drug limit.[396] In the year 2001, the Vendor Drug Program spent a total of $1.4 billion for 28.7 million claims.[397] The prescription claims information is stored in a data warehouse maintained by the National Heritage Insurance Company (NHIC) which is the claims administrator for the Texas Department of Health and Human Services.

[396] Texas Health and Human Services Commission. Texas Medicaid In Perspective. *Texas Medicaid in Perspective*. Austin; 2004:1-1-1-4.

[397] Texas Health and Human Services Commission. Overview of the Texas Medicaid Vendor Drug Program. Available at: http://www.window.state.tx.us/specialrpt/hcc2003/section2/1overview.html. Accessed November 17, 2003.

Prevalence of Hyperlipidemia in Texas

According to the Behavior Risk Factor Surveillance System survey which is an ongoing monthly telephone survey conducted by the Texas Department of Health in conjunction with the Centers for Disease Control and Prevention (CDC) reported that the overall prevalence of high cholesterol in 2002 was 31.8 percent (Table 1.6).[398] Overall, the trend in the prevalence of high cholesterol has been increasing gradually since 1990 with the sharpest rise observed between 1997 to 1999 (Figure 1). The prevalence of high cholesterol was 61.4 percent and 27.7 percent amongst CVD and non-CVD patients, respectively.[399]

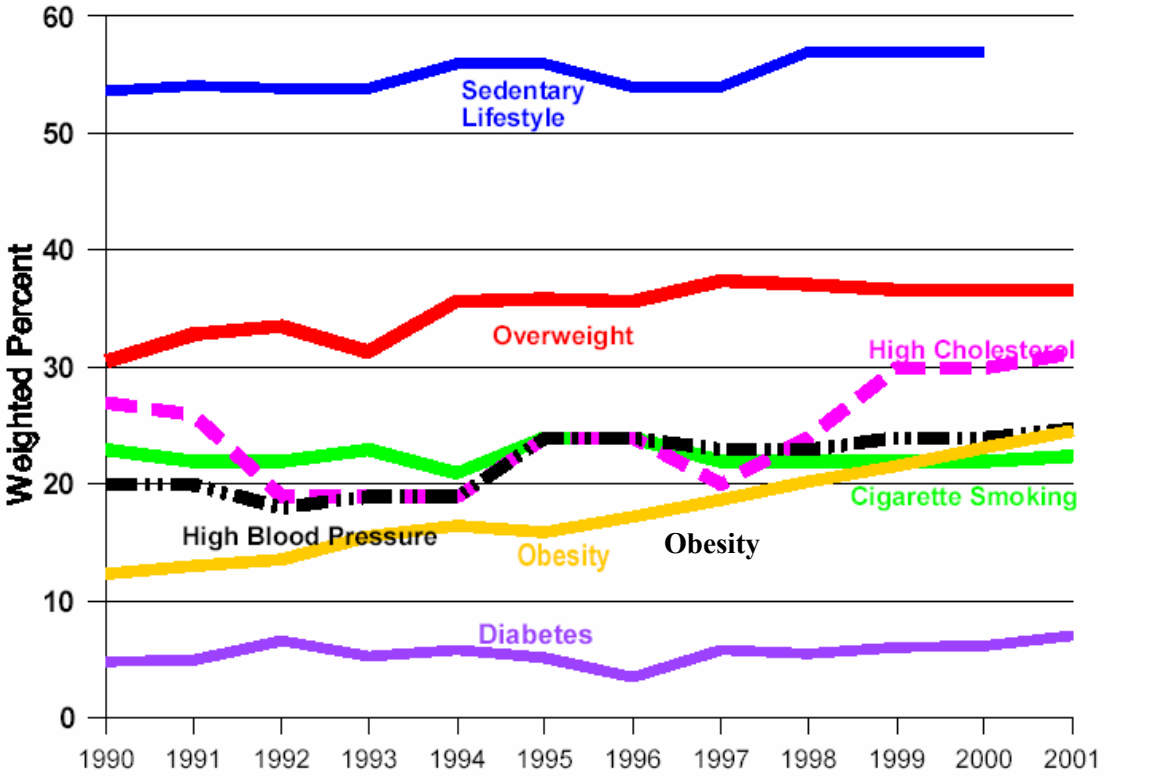
[398] Cardiovascular Health and Wellness Program. Cardiovascular Disease (CVD) in Texas: A surveillance report and program strategy 2003. *Bureau of Chronic Disease and Tobacco Prevention, Texas Department of Health*. Available at: http://www.tdh.state.tx.us/wellness/cvd/cvdsurv2003.pdf. Accessed November 17, 2003.
[399] Cardiovascular Health and Wellness Program. Cardiovascular disease in Texas: A risk factor report. 1999 Survey Data. *Bureau of Chronic Disease and Tobacco Prevention, Texas Department of Health*. Available at: http://www.tdh.state.tx.us/chronicd/cvdrep.pdf. Accessed September 15, 2003.

Table 1.6: Prevalence of High Cholesterol in Texas By Gender and Ethnicity in 2002

Demographic Characteristics	Percent Prevalence
Males	32.2%
Females	31.4%
Whites	35.2%
African Americans	29.2%
Hispanics	24.5%
Overall	**31.8%**

Source: *Bureau of Chronic Disease and Tobacco Prevention, Texas Department of Health*. Available at: http://www.tdh.state.tx.us/wellness/cvd/cvdsurv2003.pdf

Figure 1.2: Trends in Risk Factors for Cardiovascular Diseases in the State of Texas 1990-2001



Source: *Bureau of Chronic Disease and Tobacco Prevention, Texas Department of Health*. Available at: http://www.tdh.state.tx.us/wellness/cvd/cvdsurv2003.pdf.

Cardiovascular Disease in Texas

Cardiovascular diseases including ischemic heart disease, stroke and congestive heart failure were the leading causes of death in Texas claiming 55,000 lives every year.[400] In 2001, the prevalence of myocardial infarction was 3.6 percent (548,000), angina pectoris was 4.2 percent (590,000), and stroke was 2.3 percent (350,000). The prevalence of CHD by ethnicity is as follows: 8.9 percent for non-white Hispanics, 5.7 percent for African Americans and 5.4 percent for Hispanics.[401]

It was estimated that CVD cost Texas over $9 billion a year. In 1995, there were approximately 185,000 Medicare hospitalizations in which CVD was the primary diagnosis. In 1996, CVD was responsible for 40 percent of all deaths in Texas. Medicare spent a total of $500 million for CVD-related procedures in the year 1994. CVD remains the number one cause of emergency room visits.[402] CVD-related hospital discharges in the first two quarters of 1999 accounted for 18 percent of total discharges. Of these, ischemic heart disease accounted for 35 percent of all discharges, followed by

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[400] Texas Council on Cardiovascular Disease & Stroke 2001 Legislative Report. Available at: http://www.tdh.state.tx.us/wellness/cvd/cvd.htm. Accessed September 15, 2003.

[401] Cardiovascular Health and Wellness Program. Cardiovascular Disease (CVD) in Texas: A surveillance report and program strategy 2003. *Bureau of Chronic Disease and Tobacco Prevention, Texas Department of Health*. Available at: http://www.tdh.state.tx.us/wellness/cvd/cvdsurv2003.pdf. Accessed November 17, 2003.

[402] Cardiovascular Health and Wellness Program. Cardiovascular disease in Texas: A state plan with disease indicators and strategies for action. *Bureau of Chronic Disease and Tobacco Prevention, Texas Department of Health*. Available at: http://www.tdh.state.tx.us/wellness/stats/cvdrpt.pdf. Accessed November 17, 2003.

stroke (17.5%) and congestive heart failure (16.8%).[403] In the year 2001, there were approximately 136,863 CHD-related hospital discharges accounting for $4.4 billion.[404]

In the year 2002, the prevalence of CVD risk factors such as high cholesterol, blood pressure and diabetes was 31.8 percent, 25.6 percent and 7 percent, respectively. Overall there has been an increasing trend in the prevalence of CVD risk factors (Figure 1.2). There is a high prevalence of risk factors such as hypertension (63.6 percent), high blood cholesterol (61.4 percent), diabetes (23.1 percent), obesity (71.9 percent) and smoking (66.4 percent) among patients with CVD. Thus, the management of these risk factors including hyperlipidemia is important to alleviate the burden of CVD.[405]

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[403] Texas Council on Cardiovascular Disease & Stroke 2001 Legislative Report. Available at: http://www.tdh.state.tx.us/wellness/cvd/cvd.htm. Accessed September 15, 2003.

[404] Cardiovascular Health and Wellness Program. Cardiovascular Disease (CVD) in Texas: A surveillance report and program strategy 2003. *Bureau of Chronic Disease and Tobacco Prevention, Texas Department of Health*. Available at: http://www.tdh.state.tx.us/wellness/cvd/cvdsurv2003.pdf. Accessed November 17, 2003.

[405] Cardiovascular Health and Wellness Program. Cardiovascular Disease (CVD) in Texas: A surveillance report and program strategy 2003. *Bureau of Chronic Disease and Tobacco Prevention, Texas Department of Health*. Available at: http://www.tdh.state.tx.us/wellness/cvd/cvdsurv2003.pdf. Accessed November 17, 2003.

Use of Statins in the Texas Medicaid

Statins are the most widely prescribed lipid-lowering agents in the Texas Medicaid program. The Texas Medicaid program spent over $170 million on cardiovascular drugs in the year 2002.[406] Statins accounted for a number of the top 50 drugs in the Medicaid program in the year 2001, with Lipitor® 10 mg, Lipitor® 20 mg and Zocor® 20 mg tablets ranking 9th, 18th and 23rd respectively. Approximately $21 million was expended on these statin drugs in the year 2001.[407]

Criteria for Outpatient Use of Statins in the Texas Medicaid

The Texas Medicaid has review criteria for the use of HMG-CoA reductase inhibitors for outpatient use.[408] It emphasizes the use of dietary intervention prior to initiating patients on statins. If patients respond poorly to the initial doses, higher doses may be prescribed. Doses of statins drugs can be increased every four weeks based on the patient's response to the drug. Hepatic function should be monitored periodically on

[406] Pharmaceutical Benefits Under State Assistance Programs. Pharmacy program charateristics. Available at: http://www.npcnow.org/resources/PDFs/medicaid2003/03Sec4.pdf. Accessed December 14, 2004.
[407] *Texas Medicaid: Top 50 drugs cost analysis*: Center for Pharmacoeconomics Studies. The University of Texas at Austin.
[408] Drug Information Service, The University of Texas Health Science Center at San Antonio, and the College of Pharmacy*, et al.* Medicaid drug use review criteria for outpatient use: HMG-CoA reductase inhibitors. Available at: http://www.hhsc.state.tx.us/HCF/vdp/Criteria/hmg-coa.html. Accessed October 1, 2003.

initiating statin therapy. Additionally, hepatic function should also be monitored following any dose increase or addition of medications to the statin therapy that could initiate a drug interaction. Concomitant use of other lipid-lowering drugs such as gemfibrozil and niacin should be reviewed due to the increased incidence of myopathy and rhabdomylosis. Use of other drugs such as immunosuppressive agents, nefazodone, azole antifungals, macrolide antibiotics and selected protease inhibitors in conjunction with HMG-CoA reductase inhibitors should be reviewed for potential adverse events.

Rationale for the Study

Cardiovascular diseases are the leading cause of mortality and morbidity in the U.S. Epidemiologic studies support the association between hyperlipidemia and increased risk of CHD. The management of hyperlipidemia is crucial in preventing the occurrence of CHD with the treatment of hyperlipidemia being a life-long process. Statins are recommended as the first line of drug therapy in the treatment of hyperlipidemia. Texas Medicaid spent $21 million on statin drugs in the year 2001. Given the expense as well as the life-long treatment of the condition, it is important to understand the treatment of hyperlipidemia in the Texas Medicaid so that decision-makers can implement effective strategies to improve the management of the condition.

The literature review has revealed a lack of adequate management of hyperlipidemia in "real-world settings." Most of the studies conducted in clinical settings

have used data from managed care organizations. There has been no published study on the management of hyperlipidemia and adherence to cholesterol guidelines in the Texas Medicaid program. Moreover, the literature also revealed a gap in data on the management of hyperlipidemia among women and minority populations such as Hispanics and African Americans. The current research project aims to fill the gap in the literature with respect to understanding the treatment patterns, general adherence to guidelines and adherence to statin drug regimens among hyperlipidemic patients enrolled in the Texas Medicaid program.

SECTION IX

GOALS, OBJECTIVES AND HYPOTHESES OF THE STUDY

Goals

The two major goals for this study are:

1. Evaluation of statin treatment patterns and patient adherence to statin therapy; and
2. Evaluation of how well physicians follow lipid and safety monitoring guidelines.

These goals apply to the Texas Medicaid program.

Specific Objectives of the Study

The specific objectives for each of these goals follow:

Evaluation of Statin Treatment Patterns and Patient Adherence to Statin Therapy

1. To provide descriptive statistics on statin drug use and the starting dose;
2. To determine the association between statin dose prescribed at index date and CHD status at or prior to the index date;
3. To determine the use of lipid lowering drugs other than statins;
4. To determine the proportion of physicians by specialty who prescribed the initial statin therapy;
5. To provide descriptive statistics on the demographic characteristics (age, gender, and ethnicity) of hyperlipidemic patients on statins;

6. To determine the proportion of primary and secondary CHD prevention patients initiated on statins;
7. To determine the frequency distribution of patients initiated on statin therapy based on the number and type of risk factors (males > 45 years, females > 55 years, presence of hypertension and diabetes) for CHD;
8. To determine patient adherence to statin therapy based on prescription refill records;
9. To determine the persistence with statin therapy;
10. To determine the total amount reimbursed by Medicaid for statin drugs;
11. To determine if factors such as demographic characteristics (age, gender and ethnicity), type of CHD prevention, presence of diabetes, hypertension, and atherosclerotic diseases, and total number of prescriptions are predictors of adherence to statin therapy; and
12. To determine if factors such as demographic characteristics (age, gender and ethnicity), type of CHD prevention, presence of diabetes, hypertension, and atherosclerotic diseases, and total number of prescriptions are predictors of persistence to statin therapy.

Evaluation of How Well Physicians Follow Lipid and Safety Monitoring Guidelines

13. To determine lipoprotein measurements at baseline (three months prior to index date) and follow-up (three months after index date and six months thereafter) after initiating statin therapy and within three months of a change in therapy;
14. To assess the frequency and proportion of liver function tests (LFTs) to monitor adverse events in patients on statin therapy;
15. To assess the presence of LFTs following the initial dose increase;
16. To determine if factors such as demographic characteristics (age, gender and ethnicity), type of CHD prevention, presence of diabetes, hypertension, and atherosclerotic diseases, are predictors of the occurrence of lipid monitoring tests at baseline (within three months prior to start of therapy);
17. To determine if factors such as demographic characteristics (age, gender and ethnicity), type of CHD prevention, presence of diabetes, hypertension, and atherosclerotic disease, physician specialty at index date and lipid testing at baseline are predictors of the occurrence of lipid monitoring after the start of therapy (within three months, but not earlier than six weeks since the start of therapy);
18. To determine if factors such as demographic characteristics (age, gender and ethnicity), type of CHD prevention, presence of diabetes, hypertension, and atherosclerotic disease, physician specialty at index date and lipid testing at baseline are predictors of the occurrence of lipid monitoring (within three months, but not earlier than six weeks) following the initial change in statin type.;

19. To determine if factors such as demographic characteristics (age, gender and ethnicity), type of CHD prevention, presence of diabetes, hypertension, and atherosclerotic disease, physician specialty at index date and lipid testing at baseline are predictors of the occurrence of lipid monitoring (within three months, but not earlier than six weeks) following the initial change in statin dose;
20. To determine if factors such as demographic characteristics (age, gender and ethnicity), type of CHD prevention, presence of diabetes, hypertension, and atherosclerotic diseases are predictors of the occurrence of LFTs at baseline (within three months prior to start of therapy);
21. To determine if factors such as demographic characteristics (age, gender and ethnicity), type of CHD prevention, presence of diabetes, hypertension, and atherosclerotic disease, physician specialty at index date and LFTs at baseline are predictors of the occurrence of LFTs (within three months, but not earlier than six weeks) after the start of therapy; and
22. To determine if factors such as demographic characteristics (age, gender and ethnicity), type of CHD prevention, presence of diabetes, hypertension, and atherosclerotic disease, physician specialty at index date and LFTs at baseline are predictors of the occurrence of LFTs (within three months, but not earlier than six weeks) since the initial increase in statin dose.

Hypotheses for the Study Objectives

The study will test the following hypotheses:

Goal: Evaluation of Statin Treatment Patterns and Patient Adherence to Statin Therapy

Objective 2: Starting Dose and Type of CHD Prevention

Hypothesis 1: The starting dose for statin therapy for secondary prevention patients will be higher than for primary prevention patients, controlling for the type of statin.

Objective 11: Predictors of MPR

Hypothesis 2: The MPR will be higher for males than for females, controlling for age, ethnicity, presence of CHD, diabetes, hypertension, atherosclerotic diseases, and total number of prescriptions.

Hypothesis 3: The MPR will be higher for older patients than for younger patients, controlling for gender, ethnicity, presence of CHD, diabetes, hypertension, atherosclerotic disease, and total number of prescriptions.

Hypothesis 4: The MPR will be higher for non-Hispanic whites than for other ethnic groups, controlling for age, gender, presence of CHD, diabetes, hypertension, atherosclerotic diseases, and total number of prescriptions.

Hypothesis 5: The MPR will be higher for secondary prevention CHD patients than for primary prevention CHD patients, controlling for age, gender, ethnicity, presence of diabetes, hypertension, atherosclerotic diseases, and total number of prescriptions.

Hypothesis 6: The MPR will be higher for diabetics than for non-diabetics, controlling for age, gender, ethnicity, presence of CHD, hypertension, atherosclerotic diseases, and total number of prescriptions.

Hypothesis 7: The MPR will be higher for hypertensives than for non-hypertensives, controlling for age, gender, ethnicity, presence of CHD, diabetes, atherosclerotic diseases, and total number of prescriptions.

Hypothesis 8: The MPR will be higher for those patients with atherosclerotic diseases than for those without atherosclerotic diseases, controlling for age, gender, ethnicity, presence of CHD, diabetes, hypertension, and total number of prescriptions.

Hypothesis 9: The MPR will be higher for those patients on a lower number of total prescriptions other than statins than for those on a higher number of prescriptions, controlling for age, gender, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic disease.

Objective 12: Predictors of Persistence

Hypothesis 10: Females will have a higher hazard of becoming non-persistent to statin therapy than males controlling for age, ethnicity, presence of CHD, hypertension, diabetes, atherosclerotic diseases, and total number of prescriptions.

Hypothesis 11: Younger patients will have a higher hazard of becoming non-persistent to statin therapy than older patients, controlling for gender, ethnicity, presence of CHD, hypertension, diabetes, atherosclerotic diseases, and total number of prescriptions.

Hypothesis 12: Other ethnic minorities will have a higher hazard of becoming non-persistent to statin therapy than non-Hispanic whites, controlling for age, gender, presence of CHD, hypertension, diabetes, atherosclerotic diseases, and total number of prescriptions.

Hypothesis 13: Patients without CHD will have a higher hazard of becoming non-persistent to statin therapy than those with CHD, controlling for age, gender, ethnicity, presence of hypertension, diabetes, atherosclerotic diseases, and total number of prescriptions.

Hypothesis 14: Patients without diabetes will have a higher hazard of becoming non-persistent to statin therapy than those with diabetes, controlling for age, gender, ethnicity, presence of CHD, hypertension, atherosclerotic diseases, and total number of prescriptions.

Hypothesis 15: Patients without hypertension will have a higher hazard of becoming non-persistent to statin therapy than those with hypertension, controlling for age, gender, ethnicity, presence of CHD, diabetes, atherosclerotic diseases, and total number of prescriptions.

Hypothesis 16: *Patients without atherosclerotic diseases will have a higher hazard of becoming non-persistent to statin therapy than those with atherosclerotic diseases controlling for age, gender, ethnicity, presence of CHD, diabetes, hypertension, and total number of prescriptions.*

Hypothesis 17: *Patients on greater number of total prescriptions other than statins will have a higher hazard of becoming non-persistent than those on fewer prescriptions, controlling for age, gender, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases.*

Goal: Evaluation of How Well Physicians Follow Lipid and Safety Monitoring

Guidelines

Objective 16: Predictors of Lipid Testing Prior to Start of Therapy

Hypothesis 18: *The likelihood of a lipid test at baseline will be higher for males than for females, controlling for age, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases.*

Hypothesis 19: *The likelihood of a lipid test at baseline will be higher for older patients than for younger patients, controlling for gender, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases.*

Hypothesis 20: *The likelihood of a lipid test at baseline will be higher for non-Hispanic whites than for other ethnic groups, controlling for age, gender, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases.*

Hypothesis 21: *The likelihood of a lipid test at baseline will be higher for patients with CHD than for those without CHD, controlling for age, gender, ethnicity, presence of diabetes, hypertension, and atherosclerotic diseases.*

Hypothesis 22: *The likelihood of a lipid test at baseline will be higher for patients with diabetes than for those without diabetes, controlling for age, gender, ethnicity, presence of CHD, hypertension, and atherosclerotic diseases.*

Hypothesis 23: *The likelihood of a lipid test at baseline will be higher for patients with hypertension than for those without hypertension, controlling for age, gender, ethnicity, presence of CHD, diabetes, and atherosclerotic diseases.*

Hypothesis 24: The likelihood of a lipid test at baseline will be higher for patients with atherosclerotic diseases than for those without atherosclerotic diseases, controlling for age, gender, ethnicity, presence of CHD, diabetes, and hypertension.

Objective 17: Predictors of Lipid Testing After the Start of Therapy

Hypothesis 25: The likelihood of a lipid test after start of therapy will be higher for males than for females controlling for age, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.

Hypothesis 26: The likelihood of a lipid test after start of therapy will be higher for older patients than for younger patients, controlling for gender, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, physician specialty and lipid testing prior to index date.

Hypothesis 27: The likelihood of a lipid test after start of therapy will be higher for non-Hispanic whites than for other ethnic groups, controlling for age, gender, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, physician specialty and lipid testing prior to index date.

Hypothesis 28: The likelihood of a lipid test after start of therapy will be higher for patients with CHD than for those without CHD, controlling for age, gender, ethnicity, presence of diabetes, hypertension, and atherosclerotic diseases, physician specialty and lipid testing prior to index date.

Hypothesis 29: The likelihood of a lipid test after start of therapy will be higher for patients with diabetes than for those without diabetes, controlling for age, gender, ethnicity, presence of CHD, hypertension, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.

Hypothesis 30: The likelihood of a lipid test after start of therapy will be higher for patients with hypertension than for those without hypertension, controlling for age, gender, ethnicity, presence of CHD, diabetes, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.

Hypothesis 31: The likelihood of a lipid test after start of therapy will be higher for patients with atherosclerotic diseases than for those without atherosclerotic diseases, controlling for age, gender, ethnicity, presence of CHD, diabetes, and hypertension, physician specialty, and lipid testing prior to index date.

Hypothesis 32: The likelihood of a lipid test after start of therapy will be higher for patients treated by a cardiologist at index date than for those treated by other physician specialty, controlling for age, gender, ethnicity, presence of CHD, diabetes, hypertension and atherosclerotic diseases, and lipid testing prior to index date.

Hypothesis 33: The likelihood of a lipid test after start of therapy will be higher for patients with lipid tests at baseline than those without lipid tests at baseline, controlling for age, gender, ethnicity, presence of CHD, diabetes, and hypertension, atherosclerotic diseases, and physician specialty.

Objective 18: Predictors of Lipid Testing After an Initial Change in Statin Type

Hypothesis 34: The likelihood of a lipid test after an initial change in statin type will be higher for males than for females controlling for age, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.

Hypothesis 35: The likelihood of a lipid test after an initial change in statin type will be higher for older patients than for younger patients, controlling for age, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.

Hypothesis 36: The likelihood of a lipid test after an initial change in statin type will be higher for non-Hispanic whites than for other ethnic groups, controlling for age, gender, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.

Hypothesis 37: The likelihood of a lipid test after an initial change in statin type will be higher for patients with CHD than for those without CHD, controlling for age, gender, ethnicity, presence of diabetes, hypertension, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.

Hypothesis 38: The likelihood of a lipid test after an initial change in statin type will be higher for patients with diabetes than for those without diabetes, controlling for age, gender, ethnicity, presence of CHD, hypertension, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.

Hypothesis 39: The likelihood of a lipid test after an initial change in statin type will be higher for patients with hypertension than for those without hypertension, controlling for age, gender, ethnicity, presence of CHD, diabetes, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.

Hypothesis 40: The likelihood of a lipid test after an initial change in statin type will be higher for patients with atherosclerotic diseases than for those without atherosclerotic diseases, controlling for age, gender, ethnicity, presence of CHD, diabetes, and hypertension, physician specialty, and lipid testing prior to index date.

Hypothesis 41: The likelihood of a lipid test after an initial change in statin type will be higher for patients treated by a cardiologist at index date than for those treated by other physician specialty, controlling for age, gender, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, and lipid testing prior to index date.

Hypothesis 42: The likelihood of a lipid test after an initial change in statin type will be higher for patients with lipid tests at baseline than those without lipid tests at baseline, controlling for age, gender, ethnicity, presence of CHD, diabetes, and hypertension, atherosclerotic diseases, and physician specialty.

Objective 19: Predictors of Lipid Testing After an Initial Change in Statin Dose

Hypothesis 43: The likelihood of a lipid test after an initial change in statin dose will be higher for males than for females controlling for age, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.

Hypothesis 44: The likelihood of a lipid test after an initial change in statin dose will be higher for older patients than for younger patients, controlling for age, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.

Hypothesis 45: The likelihood of a lipid test after an initial change in statin dose will be higher for non-Hispanic whites than for other ethnic groups, controlling for age, gender, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.

Hypothesis 46: The likelihood of a lipid test after an initial change in statin dose will be higher for patients with CHD than for those without CHD, controlling for age, gender, ethnicity, presence of diabetes, hypertension, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.

Hypothesis 47: The likelihood of a lipid test after an initial change in statin dose will be higher for patients with diabetes than for those without diabetes, controlling for age, gender, ethnicity, presence of CHD, hypertension, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.

Hypothesis 48: The likelihood of a lipid test after an initial change in statin dose will be higher for patients with hypertension than for those without hypertension, controlling for age, gender, ethnicity, presence of CHD, diabetes, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.

Hypothesis 49: The likelihood of a lipid test after an initial change in statin dose will be higher for patients with atherosclerotic diseases than for those without atherosclerotic diseases, controlling for age, gender, ethnicity, presence of CHD, diabetes, and hypertension, physician specialty, and lipid testing prior to index date.

Hypothesis 50: The likelihood of a lipid test after an initial change in statin dose will be higher for patients treated by a cardiologist at index date than for those treated by other physician specialty, controlling for age, gender, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, and lipid testing prior to index date.

Hypothesis 51: The likelihood of a lipid test after an initial change in statin dose will be higher for patients with lipid tests at baseline than those without lipid tests at baseline, controlling for age, gender, ethnicity, presence of CHD, diabetes, and hypertension, atherosclerotic diseases, and physician specialty.

Objective 20: Predictors of LFTs Prior to Start of Therapy

Hypothesis 52: The likelihood of a LFT at baseline will be higher for males than for females, controlling for age, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases.

Hypothesis 53: The likelihood of a LFT at baseline will be higher for older patients than for younger patients, controlling for gender, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases.

Hypothesis 54: The likelihood of a LFT at baseline will be higher for non-Hispanic whites than for other ethnic groups, controlling for age, gender, presence of CHD, diabetes, hypertension, and atherosclerotic diseases.

Hypothesis 55: The likelihood of a LFT at baseline will be higher for patients with CHD than for those without CHD, controlling for age, gender, ethnicity, presence of diabetes, hypertension, and atherosclerotic diseases.

Hypothesis 56: The likelihood of a LFT at baseline will be higher for patients with diabetes than for those without diabetes, controlling for age, gender, ethnicity, presence of CHD, hypertension, and atherosclerotic diseases.

Hypothesis 57: The likelihood of a LFT at baseline will be higher for patients with hypertension than for those without hypertension, controlling for age, gender, ethnicity, presence of CHD, diabetes, and atherosclerotic diseases.

Hypothesis 58: The likelihood of a LFT at baseline will be higher for patients with atherosclerotic diseases than for those without atherosclerotic diseases, controlling for age, gender, ethnicity, presence of CHD, diabetes, and hypertension.

Objective 21: Predictors of LFTs After Start of Therapy

Hypothesis 59: The likelihood of an LFT after start of therapy will be higher for males than for females controlling for age, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, physician specialty, and presence of LFT prior to index date.

Hypothesis 60: The likelihood of an LFT after start of therapy will be higher for older patients than for younger ones, controlling for gender, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, physician specialty, and presence of LFT prior to index date.

Hypothesis 61: The likelihood of an LFT after start of therapy will be higher for non-Hispanic whites than for other ethnic groups, controlling for age, gender, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, physician specialty and presence of LFT prior to index date.

Hypothesis 62: The likelihood of an LFT after start of therapy will be higher for patients with CHD than for those without CHD, controlling for age, gender, ethnicity, presence of diabetes, hypertension, and atherosclerotic diseases, physician specialty, and presence of LFT prior to index date.

Hypothesis 63: The likelihood of an LFT after start of therapy will be higher for patients with diabetes than for those without diabetes, controlling for age, gender, ethnicity, presence of CHD, hypertension, and atherosclerotic diseases, physician specialty, and presence of LFT prior to index date.

Hypothesis 64: The likelihood of an LFT after start of therapy will be higher for patients with hypertension than for those without hypertension, controlling for age, gender, ethnicity, presence of CHD, diabetes, and atherosclerotic diseases, physician specialty and presence of LFT prior to index date.

Hypothesis 65: The likelihood of an LFT after start of therapy will be higher for patients with atherosclerotic diseases than for those without atherosclerotic diseases, controlling for age, gender, ethnicity, presence of CHD, diabetes, and hypertension, physician specialty, and presence of LFT prior to index date.

Hypothesis 66: The likelihood of an LFT after start of therapy will be higher for patients treated with a cardiologist at index date than for those treated by other physician specialty, controlling for age, gender, ethnicity, presence of CHD, diabetes, hypertension and atherosclerotic diseases, and presence of LFT prior to index date.

Hypothesis 67: The likelihood of an LFT after start of therapy will be higher for patients with LFTs at baseline than those without LFTs at baseline, controlling for age, gender, ethnicity, presence of CHD, diabetes, and hypertension, atherosclerotic diseases, and physician specialty.

Objective 22: Predictors of LFTs After an Initial Increase in Statin Dose

Hypothesis 68: The likelihood of an LFT after an initial increase in statin dose will be higher for males than for females controlling for age, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, physician specialty, and presence of LFT prior to index date.

Hypothesis 69: The likelihood of an LFT after an initial increase in statin dose will be higher for older patients than for younger patients, controlling for age, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, physician specialty, and presence of LFT prior to index date.

Hypothesis 70: The likelihood of an LFT after initial increase in statin dose will be higher for non-Hispanic whites than for other ethnic groups, controlling for age, gender, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, physician specialty, and presence of LFT prior to index date.

Hypothesis 71: The likelihood of an LFT after an initial increase in statin dose will be higher for patients with CHD than for those without CHD, controlling for age, gender, ethnicity, presence of diabetes, hypertension, and atherosclerotic diseases, physician specialty, and presence of LFT prior to index date.

Hypothesis 72: The likelihood of an LFT after an initial increase in statin dose will be higher for patients with diabetes than for those without diabetes, controlling for age, gender, ethnicity, presence of CHD, hypertension, and atherosclerotic diseases, physician specialty, and presence of LFT prior to index date.

Hypothesis 73: The likelihood of an LFT after an initial increase in statin dose will be higher for patients with hypertension than for those without hypertension, controlling for age, gender, ethnicity, presence of CHD, diabetes, and atherosclerotic diseases, physician specialty, and presence of LFT prior to index date.

Hypothesis 74: The likelihood of an LFT after an initial increase in statin dose will be higher for patients with atherosclerotic diseases than for those without atherosclerotic diseases, controlling for age, gender, ethnicity, presence of CHD, diabetes, and hypertension, physician specialty, and presence of LFT prior to index date.

Hypothesis 75: The likelihood of an LFT after an initial increase in statin dose will be higher for patients treated by a cardiologist at index date than for those treated by other physician specialty, controlling for age, gender, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, and presence of LFT prior to index date

Hypothesis 76: The likelihood of an LFT after start of therapy will be higher for patients with LFTs at baseline than those without LFTs at baseline, controlling for age, gender, ethnicity, presence of CHD, diabetes, and hypertension, atherosclerotic diseases, and physician specialty.

CHAPTER TWO

METHODOLOGY

This chapter presents a description of the study design, study population, data sources, study variables and the data analysis plan.

STUDY DESIGN AND POPULATION

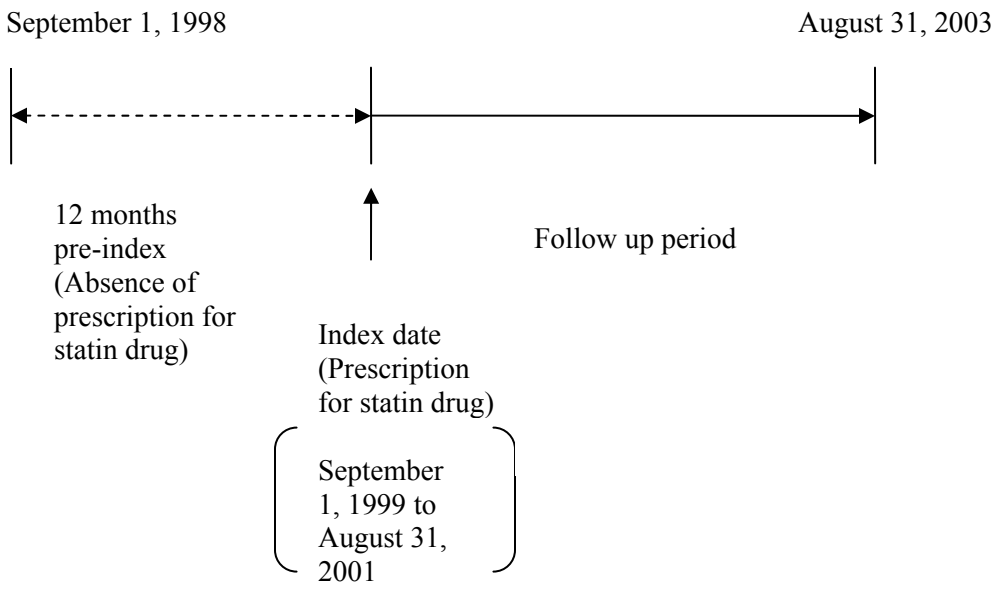
This study was a retrospective cohort analysis using the Texas Medicaid database. The study population included patients who had started taking a statin drug and were between ages of 21 and 64 years and who were eligible for Texas Medicaid benefits between September 1, 1998 to August 31, 2003. Recipients over 65 years old were not included in the analysis since the researcher was not able to obtain complete medical claims for patients who had dual eligibility (i.e., some patients were covered under both the Medicaid and Medicare programs).

Identification of Study Subjects

The design was a retrospective cohort study of statin users in the Texas Medicaid system. The study period was from September 1, 1998 to August 31, 2003. Patients who filled at least one prescription for a statin (atorvastatin, fluvastatin, lovastatin, pravastatin or simvastatin) between September 1, 1999 and August 31, 2001 were included. Patients on cerivastatin were excluded from the study since this drug was recalled in 2001. The patient's index date was defined as the date of first pharmacy claim for any statin

between September 1, 1999 and August 31, 2001. An explanation of the timeline for the study is presented in Figure 2.1. To ensure the inclusion of only new statin users, enrollees who had at least one prescription for any drug, but no statin prescriptions in the twelve-month period prior to the index date were included in the study. Individuals were followed for two years from the index date. Individuals should have had one and two years of continuous enrollment prior to and after the index date, respectively, to be included in the study. Enrollment in the Medicaid system was determined from the eligibility start and end dates present in the Texas Medicaid Eligibility File. In addition, patients should have had at least two fills of statin drugs on separate dates within the first year in order to be included in the study.

Figure 2.1: Time-frame for the Study



DATA SOURCES

Data were collected from Texas Medicaid claims data files: (1) Medicaid Eligibility File; (2) Texas Medicaid Medical Claims File; (3) Texas Medicaid Prescription Claims File; and (4) Texas State Board of Medical Examiners database. The databases were used to extract information on Medicaid eligibility of statin users, their demographic characteristics, statin use, clinical conditions, lipid and hepatic function monitoring, and physician demographics characteristics. The information contained in each of the three Medicaid data files is listed below.

The Texas Medicaid Eligibility File

A unique client identification number was assigned to each Medicaid patient in the eligibility file and it was used to link the prescription and the medical claims databases. Table 2.1 presents information found in the Texas Medicaid Eligibility File.

Table 2.1: Texas Medicaid Eligibility File Information

1. Unique client identification number
2. Date of birth
3. Gender of patient
4. Ethnicity of patient
5. Eligibility start date
6. Eligibility end date

The Texas Medicaid Medical Claims File

Only the medical claims from fee-for-service (FFS) and primary care case management (PCCM) Medicaid recipients were extracted and included in the Texas Medicaid Medical Claims file. This was done out of concern that the managed care Medicaid claims were incomplete due to the capitation payment method of the managed care systems. Table 2.2 lists the information included in the Medical Claims File.

Table 2.2: Texas Medicaid Medical Claims File Information

1. Unique client identification number
2. Performing provider number
3. Diagnosis 1
4. Diagnosis 2
5. Diagnosis 3
6. Diagnosis 4
7. Diagnosis 5
8. Procedure code
9. Beginning date of service for the claim
10. Last date of service covered by the claim
11. Place of service (e.g. emergency room, inpatient hospital, physician's office, etc.)
12. Type of service (e.g. surgery, consultation, anesthesia etc.)
13. Admit date
14. Admit diagnosis
15. Type of admission (e.g. emergency, elective, newborn etc.)
16. Days of service
17. Medicaid payment for the service
18. County code
19. DRG code
20. Procedure modifier code

The Texas Medicaid Prescription Claims File

Medicaid reimbursed prescription claims records of individuals identified to be eligible for the study were extracted from the Texas Medicaid Vendor Drug paid claims database. Table 2.3 presents information included in the prescription claims file.

Table 2.3: Texas Medicaid Prescription Claims File Information

1. Unique client identification number
2. Pharmacy provider number
3. Date prescription filled
4. Number of refills authorized
5. Prescribing physician number
6. Prescribing physician specialty
7. Amount reimbursed by Medicaid
8. National Drug Code (NDC) (unique code for drugs that identifies the labeler/vendor, product, and package size)
9. Generic product sequence code (unique product code provided by First DataBank and assigned to all products having the same active ingredient and dosage form regardless of manufacturer)
10. Generic product identifier (GPI) (classified drugs with respect to the compound regardless of the strength)
11. Quantity dispensed
12. Day's supply
13. Strength
14. Age of patient at prescription dispensing
15. Gender of patient

APPROVAL TO USE HUMAN SUBJECTS

The study did not involve direct contact with patients and the information was de-identified. However, since health information of subjects from the Medicaid database was used for the study, it was necessary to file a petition to The University of Texas Institutional Review Board to obtain a waiver of informed consent. The study received approval for a waiver of informed consent from the Institutional Review Board at the University of Texas at Austin (UT-IRB #2003-09-0132). As noted in the request for a waiver, the use of health information for this study involved no more than a minimal risk to the privacy of individuals since the study was a retrospective analysis of claims database and the researcher did not have access to personal names, social security numbers or addresses of the Medicaid patients.

The Medicaid unique identification number was used only to link the pharmacy claims with the healthcare utilization claims and was replaced by alpha numeric characters which were linked to the identification number. The de-identified records were stored on the Center for Pharmacoeconomic Studies server computer and only the principal investigator, the supervisor of the dissertation (Marvin D. Shepherd, Ph.D.) and the associate director of the Center for Pharmacoeconomic Studies (Michael T. Johnsrud, Ph.D.) had access to these de-identified records. Access to the data was password protected.

STUDY VARIABLES

All dependent and independent variables included in the study are defined in Table 2.4. The operationalization of the study variables is explained later in this chapter.

Table 2.4: Explanation of the Variables Used in the Study

Variable	Explanation
Age	Age was reported as the age of the person at the index date. Only those patients who were between the ages of 21-62 years at the index date were included. Age was analyzed as a continuous variable.
Gender	Gender was indicated as "male or "female."
Ethnicity	Ethnicity was coded as non-Hispanic whites, non-Hispanic blacks, Hispanics, Asians or Pacific Islanders, and American Indians or Alaskan Natives.
Physician specialty	Information on the specialty of the prescribing physician at index date was obtained from the Texas State Board of Medical Examiners (TSBME) database. The physician's unique license number was used to link the Medicaid file with the database obtained from TSBME. Specialty of the physician prescribing the statin at the index date was classified into three groups: general practice/family practice and internal medicine; cardiologists; and others.
Physician Demographics	Demographic characteristics such as age, gender and years of licensure of the physician prescribing the statin at index date was determined from the TSBME database.
Type of CHD prevention	Patients were classified as primary or secondary prevention patients based on the diagnosis for established CHD in the year prior to or at the index date. The development of a new diagnosis for CHD during the follow-up period was also assessed.
Diabetes	Presence or absence of diabetes as a risk factor for CHD in the year prior to or at the index date was coded as "yes" or "no," respectively. The development of a new diagnosis for diabetes during the follow-up period was also assessed.
Total number of prescriptions	The total number of unique prescriptions (other than statins) that the patient was on during the two-year follow-up period was assessed using the Generic Product Identifier (GPI) that classifies products based on the compound rather than the strength.

Table 2.4: Explanation of the Variables in the Study (continued)

Variable	Explanation
Hypertension	Presence or absence of hypertension as a risk factor for CHD in the year prior to or at the index date was coded as "yes" or "no," respectively. The development of a new diagnosis for hypertension during the follow-up period was also assessed.
Other atherosclerotic diseases	Presence or absence of other atherosclerotic disease including atherosclerosis, stroke and peripheral vascular disease was assessed prior to or at the index date and during the follow-up period and was coded as "yes" or "no," respectively.
Compliance measures	Two measures were used to assess compliance to statins: • Medication Possession Ratio (MPR) ➢ The MPR was calculated as a ratio of the sum of the days' supply dispensed (except supply at the last refill date) and the sum of the days between the first and the last prescription • Persistence ➢ Persistence was expressed as number of days of statin therapy before discontinuation. Discontinuation was defined as failure to refill the prescription within 60 days of exhausting the last supply. A sensitivity analysis was conducted using a gap of 45 days.
Lipid measurements	The presence of a lipid test was assessed at: • Baseline (within three months prior to initiation of statin therapy). • Follow-up (within three months, but not earlier than six weeks, after initiation of statin therapy and six months, thereafter). • Within three months, but not earlier than six weeks, following initial change in dose of statin drug. • Within three months, but not earlier than six weeks, following the initial change in statin type. The presence or absence of the test was coded as "yes" or "no," respectively.
Liver function tests (LFTs)	The presence of LFT was assessed at: • Baseline (within three months prior to initiation of statin therapy). • Follow-up (within three months but not earlier than six weeks after initiation of statin therapy and six months thereafter). • Within three months but not earlier than six weeks, following an initial increase in statin dose. The presence or absence of the test was coded as "yes" or "no," respectively.

MEASURES OF VARIABLES

A description of how each of the variables described in Table 2.4 was operationalized is presented in this section.

Type of Coronary Heart Disease (primary or secondary) Prevention Patients

Patients were classified as either primary or secondary prevention patients at the index date based on the diagnosis of coronary heart disease (CHD) in the year prior to or at the index date. The development of a new diagnosis for CHD during the follow-up period was also assessed. Primary prevention patients were defined as patients without a history of established CHD whereas secondary prevention patients were those who had a history of established CHD including indications for acute myocardial infarction, angina, chronic ischemic heart disease, history of percutaneous coronary intervention or coronary artery bypass graft. Primary and secondary prevention patients were differentiated based on the diagnostic codes (*International Classification of Diseases, 9th Revision, Clinical Modifications [ICD-9-CM]*) (Table 2.5) and procedural codes (*Current Procedural Terminology [CPT]*) (Table 2.6).

Table 2.5: Description of Diagnostic Codes to Identify the Presence of Established CHD

ICD-9-CM Codes	Description
410.xx	Acute myocardial infarction
411.xx	Other acute or subacute forms of ischemic heart disease
412	Old myocardial infarction
413	Angina pectoris
414.xx	Other forms of chronic ischemic heart disease
36.0x	Percutaneous coronary intervention
36.1x	Coronary artery bypass graft (CABG)

Table 2.6: Description of Procedural Codes to Identify the Presence of CHD

CPT codes	Description
33510-33516	Coronary artery bypass-venous grafting only procedures
33517-33530	Coronary artery bypass-combined arterial-venous grafting
33533-33536	Coronary artery bypass-arterial grafting
33572	Open coronary endarterectomy
92975	Thrombolysis, coronary; by intracoronary infusion, including selective coronary angiography
92977	Thrombolysis, coronary; by intravenous infusion
92980-92981	Transcatheter placement of an intracoronary stent(s)
	Other forms of chronic ischemic heart disease
92982	Percutaneous transluminal coronary balloon angioplasty; single vessel
92984	Percutaneous transluminal coronary balloon angioplasty; each additional vessel
92995	Percutaneous transluminal coronary atherectomy; by mechanical or other method, with or without balloon angioplasty; single vessel
92996	Percutaneous transluminal coronary atherectomy; by mechanical or other method, with or without balloon angioplasty; each additional vessel

Presence of Risk Factors and Atherosclerotic Diseases

The presence of atherosclerotic diseases such as stroke, atherosclerosis, and peripheral vascular disease was also assessed. In addition, the presence of hypertension and diabetes as risk factors for CHD in the database was determined. The data were obtained from the medical claims file. The presence of conditions such atherosclerotic diseases, diabetes and hypertension was assessed in the year prior to or at the index date and during the follow-up period. The ICD-9-CM codes are listed in Tables 2.7 and 2.8. The presence of risk factors and atherosclerotic diseases for each patient was assessed.

Table 2.7: Description of Diagnostic Codes to Identify the Presence of Atherosclerotic Disease

ICD-9-CM Codes	Description
Atherosclerosis	
429.2	Cardiovascular disease, unspecified Arteriosclerotic CVD Cardiovascular arteriosclerosis Cardiovascular disease: degeneration, disease, sclerosis (with mention of arteriosclerosis)
440.xx 440.0 440.1 440.2 440.3 440.8 440.9	Atherosclerosis Of aorta Of renal artery Of native arteries of the extremities Of bypass graft of extremities Of other specified arteries Generalized and unspecified atherosclerosis
Stroke	
433.xx	Occlusion and stenosis of precerebral arteries
434.xx	Occlusion of cerebral arteries
435.xx	Transient cerebral ischemia
436.xx	Acute, but ill-defined, cerebrovascular disease
Peripheral Vascular Disease	
443.xx	Other peripheral vascular disease

Table 2.8: ICD-9-CM Codes to Identify Hypertension and Diabetes as Risk Factors for CHD

ICD-9 codes	Description
401.x, 402.xx, 403.xx, 404.xx, 362.11, 437.2	Hypertension
250.xx, 362.01, 362.01, 366.41	Diabetes
362.01	Background diabetic retinopathy
362.02	Proliferative diabetic retinopathy
366.41	Diabetic cataract
362.11	Hypertension retinopathy

Lipid Measurements and Monitoring for Adverse Effects

The ATP II guidelines recommend lipid monitoring prior to initiating drug therapy as well as follow-up measurements. Based on the guidelines, it is important to have a minimum of two lipoprotein measurements during one to two months of diet therapy prior to initiating the drug therapy. After starting drug therapy, the first lipoprotein measurement is recommended at six to eight weeks. Once the target LDL levels are reached, patients should be monitored every eight to twelve week intervals through 52 weeks. After a year of therapy, once the LDL levels are attained, monitoring of lipids and adverse effects should be conducted at four- to six-month intervals. Monitoring for toxicity should be carried out at the same time as lipid and lipoprotein

measurements.[409] In addition, the ATP III guidelines recommend lipid monitoring within six to eight weeks following a change in drug regimen.[410]

For the purpose of this study, lipid measurement included measurement of LDL levels since the guidelines recommend the assessment of LDL levels for the attainment of lipid goals. The presence of a LDL monitoring test will be identified with the help of CPT codes (Table 2.9) in the medical claims file. The presence of a CPT code for a lipid panel would indicate LDL measurement since this includes a separate measurement for LDL. The presence of CPT codes for total cholesterol (TC), high density lipoprotein (HDL) and very low-density lipoprotein (VLDL) on the same date would indicate assessing the LDL levels since the LDL levels can be calculated using the formula below. Similarly, the presence of CPT codes for TC, HDL and triglycerides (TG) on the same date would also indicate LDL monitoring. The LDL levels can be calculated using the Friedwall equation as follows:

LDL = TC –HDL-VLDL or LDL = TC –HDL – (TG/5)

Similarly, adverse event monitoring will be identified based on the presence of liver function tests (Table 2.10). LDL measurements and tests for monitoring for adverse events were assessed as two separate variables.

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[409] *Second report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II).* Bethesda (MD): U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Heart, Lung and Blood Institute; 1993. NIH Publication No: 93-3095.
[410] Grundy SM, Becker DM, Clark L, et al. Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *Journal of the American Medical Association.* 2001;285(19):2486-2497.

Table 2.9: Description of Procedural Codes for Lipid Monitoring Tests

CPT codes	Description
80061	Lipid Panel
82465	Cholesterol, Serum, Total
83718	Lipoprotein, Direct Measurement, High Density Cholesterol
83719	Lipoprotein, Direct Measurement; VLDL Cholesterol
83721	Lipoprotein, Direct Measurement; LDL Cholesterol
84478	Triglycerides

Table 2.10: Description of Procedural Codes for Liver Function Tests

CPT codes	Description
80076	Hepatic Function Panel
84450	Transferase; aspartate amino (AST) (SGOT)
84460	Alanine amino; (ALT) (SGPT)

Lipid Measurements

Lipid measurements were assessed using the medical claims data. The NCEP guidelines recommend lipid measurements prior to the start of therapy, following the start of therapy and lipid monitoring thereafter.[411,412] For the purpose of the present study, baseline LDL monitoring was assessed within three months prior to the initiation of statin

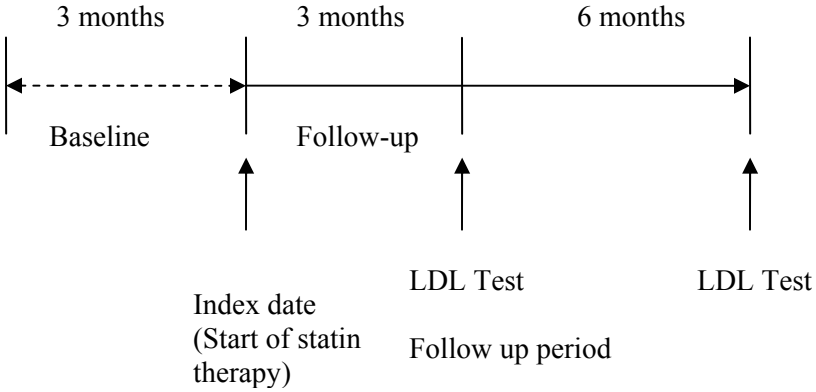
[411] Grundy SM, Becker DM, Clark L, et al. Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *Journal of the American Medical Association.* 2001;285(19):2486-2497.

[412] *Second report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II).* Bethesda (MD): U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Heart, Lung and Blood Institute; 1993. NIH Publication No: 93-3095.

therapy (index date). Follow-up LDL monitoring was assessed within three months but not earlier than six weeks, after the initiation of statin therapy and within six months thereafter. In addition, LDL monitoring within three months following an initial change in dose or type of statin drug was also evaluated. A patient should have had a minimum of two lipid tests in a nine month follow-up period from the start of statin therapy. LDL measurements were assessed as follows:

1. *LDL monitoring before the start of therapy*: LDL monitoring was assessed three months prior to the start of therapy.
2. *LDL monitoring at start of therapy:* LDL monitoring at the start of therapy was assessed within three months at the initiation of statin therapy but not earlier than six weeks, and six months from the first LDL test. For example, if the first LDL test was conducted at time T1, then a second LDL test should be conducted between the time period from T1 to T1+180 days.

Fig 2.2: LDL Monitoring at the Start of Statin Therapy for Patients without a Change in Therapy



3. *LDL monitoring following initial change in dose of statin:* The presence of a LDL test within three months but not earlier than six weeks following an initial change in dose of statin therapy was assessed. The proportion of patients with LDL tests following an initial change in dose of statin therapy was determined.
4. *LDL monitoring following an initial change in the type of statin:* The presence of a lipid test within three months but not earlier than six weeks following an initial change in the type of statin therapy was assessed. The proportion of patients with lipid tests following an initial change in type of statin therapy was determined.

In addition to the above measurements, the proportions of patients with LDL tests six months and a year prior to the start of therapy and six months and a year after the start of therapy were assessed.

Monitoring for Adverse Effects

The occurrence of liver function tests (LFTs) was monitored in the medical claims data. Baseline LFTs were assessed within three months prior to the initiation of statin therapy (index date). Follow-up LFTs were assessed within three months but not earlier than six weeks after the initiation of statin therapy and within six months thereafter. In addition, LFTs within three months following an initial increase in the dose of the statin drug were also evaluated. A patient should have had a minimum of two LFTs in a nine month follow-up period from the start of statin therapy. Hepatic function monitoring was assessed as follows:

1. *Monitoring of LFTs at baseline:* Monitoring for LFT was assessed three months prior to the start of therapy.
2. *Monitoring of LFTs at start of therapy:* LFTs at the start of therapy were assessed within three months at the initiation of statin therapy but not earlier than six weeks and six months from the first LFT test. For example, if the first LFT was conducted at time T1, then the second LFT should be conducted between the time period from T1 to T1+180 days.
3. *Monitoring of LFTs following an initial increase in dose of statin:* The presence of LFTs within three months but not earlier than six weeks following an initial increase in dose of statin therapy were assessed. The proportion of patients with LFTs following an increase in statin dose was determined.

In addition to the above measurements, LFT monitoring six months and a year prior to the start of therapy and six months and a year after the start of therapy was also evaluated.

Physician Characteristics

Information on the specialty of the prescribing physician at index date was obtained from the Texas State Board of Medical Examiners (TSBME). The physician's unique license number was used to link the Medicaid file with the database obtained from TSBME. The physician specialty was classified into three groups: general practice/family practice and internal medicine; cardiologists; and others. Demographic

characteristics such as the physicians' age, gender and years of licensure were obtained from the TSBME database.

Compliance Measures

Compliance with statin therapy was calculated using prescription refill dates and days' supply data present in the prescription claims file. Compliance was calculated for those patients with at least two fills of the prescription for statin drugs on two different dates. The medication possession ratio was calculated by summing the number of days' supply of medication dispensed (except the supply on the last refill date), and dividing this by the number of days between the initial and the last statin prescription fill date.

$$\text{MPR} = \frac{\text{Sum of days' supply dispensed (except supply at last refill date)}}{\text{Sum of days between the first and the last prescription}}$$

This method assumes that patients cannot be compliant unless they have an adequate supply of medications. This MPR method has been previously validated by Steiner et al.[413] and has been used previously to measure compliance with antihyperlipidemic drugs therapy regimens.[414,415] An MPR ratio of 80 percent adherence

[413] Steiner JF, Koepsell TD, Fihn SD*, et al.* A general method of compliance assessment using centralized pharmacy records: Description and validation. *Medical Care.* 1988;26(8):814-823.
[414] Sung JCY, Nichol MB, Venturini F*, et al.* Factors affecting patient compliance with antihyperlipidemic medication in an HMO population. *American Journal of Managed Care.* 1998;4(10):1421-1430.
[415] Omar MA. *An evaluation of the clinical and economic outcomes associated with switching hyperlipidemic patients to preferred statin therapy in the United States Department of Defense*. Dissertation: Department of Pharmacy Practice and Administration, University of Texas at Austin; 2001.

to the medication regimen is considered as a standard since this threshold is used conventionally in clinical trials.[416]

Although MPR has been used extensively in the literature to assess compliance, it is important to acknowledge its limitations.[417] Firstly, the calculation of an MPR is limited based on the time length involved. Patients with shorter follow-up periods would inflate the compliance measures since they have been observed for fewer days and have a lesser chance to discontinue their medications compared to patients who have longer periods of follow-up. Secondly, the compliance patterns during the entire follow-up period cannot be evaluated using the MPR since the MPR summarizes the compliance to medications as a single number.[418]

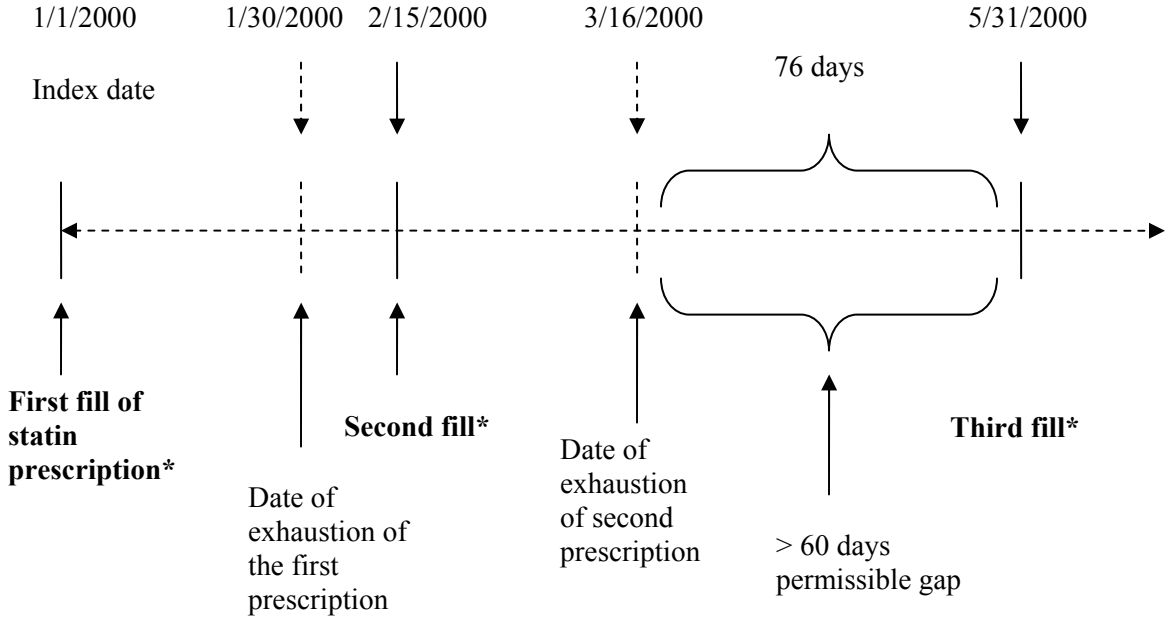
Owing to the limitations of the MPR, persistence of statin therapy using survival analysis was assessed in addition to the MPR. Persistence measures how long the patient remains on therapy and is defined as total days from index prescription fill date until termination of statin therapy.[419] Patients were classified as being persistent if they did not discontinue therapy. Patients failing to refill their prescriptions within 60 days of exhausting their last supply were characterized as having discontinued their statin

[416] Insull W. The problem of compliance to cholesterol altering therapy. *Journal of Internal Medicine.* 1997;241(4):317-325.
[417] Johnson ES, Mozaffari E. Measuring patient persistency with drug therapy using methods for the design and analysis of natural history studies. *American Journal of Managed Care.* 2002;8(10):S249-S254.
[418] Johnson ES, Mozaffari E. Measuring patient persistency with drug therapy using methods for the design and analysis of natural history studies. *American Journal of Managed Care.* 2002;8(10):S249-S254.
[419] Johnson ES, Mozaffari E. Measuring patient persistency with drug therapy using methods for the design and analysis of natural history studies. *American Journal of Managed Care.* 2002;8(10):S249-S254.

therapy. Days of persistency was the time between the index prescription fill date and the date of last prescription preceding a 60-day gap. A sensitivity analysis was conducted using a gap of 45 days.

An example of the measurement of persistence is shown Figure 2.3. Consider a patient whose index date for the first statin prescription is January 1, 2000. The patient is dispensed a 30 days supply of a statin on January 1, 2000. Based on the days supply, the patient should run out of medication by January 30, 2000 if the patient is taking the statin once a day as prescribed. The next refill date of the prescription for the same patient is February 15, 2000 for a 30-day supply of the statin. At this point, the patient is still persistent with the statin therapy since the patient refilled the prescription within 60 days of the exhaustion of the last prescription. The patient gets the third prescription fill of a 30 days supply of the statin on May 31, 2000. The patient at this point is considered to have discontinued the therapy since the gap between the date of exhaustion of the last prescription (March 16, 2000) and the date of the third refill (May 31, 2000) exceeded the 60-day permissible gap to be persistent. The patient was considered to be persistent from January 1, 2000 to February 15, 2000 and the total days of persistency were 46 days.

Fig 2.3: Example of Measurement of Persistence with Statin Therapy in Days



*****_All supply is assumed to be for 30 days_

Cost of Statin Drugs

The total amount reimbursed by Texas Medicaid for statin drugs was calculated by summing the total amount spent on each patient for the two year follow-up period. The number of statin prescriptions filled per year was assessed and the total amount reimbursed by Medicaid for statin drugs per patient per year was calculated. In addition, the cost per member per month reimbursed was calculated.

STATISTICAL ANALYSIS

Data manipulation and statistical analyses were conducted using Microsoft Access and Statistical Packages for Social Sciences (SPSS) v11.0. The "a priori" level of significance of 0.05 was used for all statistical tests conducted. All tests were two-tailed unless otherwise specified. A description of statistical tests conducted for each objective and related hypothesis follows.

Evaluation of Statin Treatment Patterns and Patient Adherence to Statin Therapy

Appropriate descriptive statistics (frequency, mean, standard deviation) were used to examine the demographic characteristics (age, gender, and ethnicity) of the subjects. Frequency distributions of the type and starting dose of the statin drugs and the specialty of the index statin prescriber were presented. Similarly, frequency distributions were obtained for the type of CHD prevention patients, and type of CHD risk factors and presence of atherosclerotic diseases. The proportion of patients who experienced an initial change in therapy with respect to dose and type of statin was calculated.

The predictors of compliance with statin therapy were determined with the help of multiple regression and Cox regression models. The predictor variables in the model included age, gender, ethnicity, presence of CHD, diabetes or hypertension as risk factors, presence of atherosclerotic disease (stroke, atherosclerosis and peripheral vascular disease) and total number of prescription other than statins during the two-year follow-up period. Survival analysis was used to assess the time to statin discontinuation. A Cox proportional hazards model was used to assess the predictors of persistence.

The coding scheme for the predictor variables is shown in Table 2.11.

Table 2.11: Coding of Variables Included in Regression Models

Variables	**Variable Code**
Age	Age at the index date
Gender	1=Male; 2=Female
Ethnicity	1=Non-Hispanic whites; 2=Non-Hispanic blacks; 3=Hispanics; 4=Asians or Pacific Islanders; and 5=American Indians or Alaskan Natives.
CHD	1 = No disease; 2 = Disease prior to index date; 3 = Disease developed during follow-up period.
Presence of diabetes	1 = No disease; 2 = Disease prior to index date; 3 = Disease developed during follow-up period.
Presence of hypertension	1 = No disease; 2 = Disease prior to index date; 3 = Disease developed during follow-up period.
Presence of atherosclerotic disease	1 = No disease; 2 = Disease prior to index date; 3 = Disease developed during follow-up period.
Total number of prescriptions	Total number of unique prescriptions, other than statins, that the patients were on for the two-year follow-up period.

Evaluation of How Well Physicians Follow Lipid and Safety Monitoring Guidelines

Descriptive statistics were used to determine the frequency of lipid monitoring tests and liver function tests at baseline (within three months prior to the index date) and follow-up (within three months after initiation of statin therapy) and six months thereafter and also following initial changes in the medication regimen. The proportion of patients with lipid tests and liver function tests was evaluated. Logistic regression analysis was used to assess the predictors of the occurrence of LDL tests and LFTs.

Statistical Tests for the Study Hypotheses

The statistical tests for the study hypotheses are tabulated in Table 2.12.

Table 2.12: Proposed Statistical Tests for the Study Hypotheses

Study Hypotheses	**Statistical Test**
Goal : Evaluation of Statin Treatment Patterns and Adherence to Statin Therapy	
Hypothesis 1: The starting dose for statin therapy for secondary prevention patients will be higher than for primary prevention patients, controlling for the type of statin.	Chi-square analysis
Hypothesis 2: The MPR will be higher for males than for females, controlling for age, ethnicity, presence of CHD, diabetes, hypertension, atherosclerotic diseases, and total number of prescriptions.	Multiple regression analysis
Hypothesis 3: The MPR will be higher for older patients than for younger patients, controlling for gender, ethnicity, presence of CHD, diabetes, hypertension, atherosclerotic disease, and total number of prescriptions.	Multiple regression analysis
Hypothesis 4: The MPR will be higher for non-Hispanic whites than for other ethnic groups, controlling for age, gender, presence of CHD, diabetes, hypertension, atherosclerotic diseases, and total number of prescriptions.	Multiple regression analysis
Hypothesis 5: The MPR will be higher for secondary prevention CHD patients than for primary prevention CHD patients, controlling for age, gender, ethnicity, presence of diabetes, hypertension, atherosclerotic diseases, and total number of prescriptions.	Multiple regression analysis
Hypothesis 6: The MPR will be higher for diabetics than for non-diabetics, controlling for age, gender, ethnicity, presence of CHD, hypertension, atherosclerotic diseases, and total number of prescriptions.	Multiple regression analysis
Hypothesis 7: The MPR will be higher for hypertensives than for non-hypertensives, controlling for age, gender, ethnicity, presence of CHD, diabetes, atherosclerotic diseases, and total number of prescriptions.	Multiple regression analysis

Table 2.12: Proposed Statistical Tests for the Study Hypotheses (continued)

Study Hypotheses	Statistical Test
Goal : Evaluation of Statin Treatment Patterns and Adherence to Statin Therapy	
Hypothesis 8: The MPR will be higher for those patients with atherosclerotic diseases than for those without, atherosclerotic diseases controlling for age, gender, ethnicity, presence of CHD, diabetes, hypertension, and total number of prescriptions.	Multiple regression analysis
Hypothesis 9: The MPR will be higher for those patients on a lower number of total prescriptions other than statins than for those on a higher number of prescriptions, controlling for age, gender, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic disease.	Multiple regression analysis
Hypothesis 10: Females will have a higher hazard of becoming non-persistent to statin therapy than males controlling for age, ethnicity, presence of CHD, hypertension, diabetes, atherosclerotic diseases, and total number of prescriptions.	Cox regression analysis
Hypothesis 11: Younger patients will have a higher hazard of becoming non-persistent to statin therapy than older patients, controlling for gender, ethnicity, presence of CHD, hypertension, diabetes, atherosclerotic diseases, and total number of prescriptions.	Cox regression analysis
Hypothesis 12: Other ethnic minorities will have a higher hazard of becoming non-persistent to statin therapy than non-Hispanic whites, controlling for age, gender, presence of CHD, hypertension, diabetes, atherosclerotic diseases, and total number of prescriptions.	Cox regression analysis
Hypothesis 13: Patients without CHD will have a higher hazard of becoming non-persistent to statin therapy than those with CHD, controlling for age, gender, ethnicity, presence of hypertension, diabetes, atherosclerotic diseases, and total number of prescriptions.	Cox regression analysis
Hypothesis 14: Patients without diabetes will have a higher hazard of becoming non-persistent to statin therapy than those with diabetes, controlling for age, gender, ethnicity, presence of CHD, hypertension, atherosclerotic diseases, and total number of prescriptions.	Cox regression analysis

Table 2.12: Statistical Tests for the Study Hypotheses (continued)

Study Hypotheses	Statistical Test
Goal : Evaluation of Statin Treatment Patterns and Adherence to Statin Therapy	
Hypothesis 15: Patients without hypertension will have a higher hazard of becoming non-persistent to statin therapy than those with hypertension, controlling for age, gender, ethnicity, presence of CHD, diabetes, atherosclerotic diseases, and total number of prescriptions.	Cox regression analysis
Hypothesis 16: Patients without atherosclerotic diseases will have a higher hazard of becoming non-persistent to statin therapy than those with atherosclerotic diseases controlling for age, gender, ethnicity, presence of CHD, diabetes, hypertension, and total number of prescriptions.	Cox regression analysis
Hypothesis 17: Patients on greater number of total prescriptions other than statins will have a higher hazard of becoming non-persistent than those on fewer prescription, controlling for age, gender, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases.	Cox regression analysis
Goal: Evaluation of How Well Physicians Follow Lipid and Safety Monitoring Guidelines: Lipid Monitoring at Baseline	
Hypothesis 18: The likelihood of a lipid test at baseline will be higher for males than for females, controlling for age, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases.	Logistic regression analysis
Hypothesis 19: The likelihood of a lipid test at baseline will be higher for older patients than for younger patients, controlling for gender, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases.	Logistic regression analysis
Hypothesis 20: The likelihood of a lipid test at baseline will be higher for non-Hispanic whites than for other ethnic groups, controlling for age, gender, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases.	Logistic regression analysis
Hypothesis 21: The likelihood of a lipid test at baseline will be higher for patients with CHD compared to those without CHD, controlling for age, gender, ethnicity, presence of diabetes, hypertension, and atherosclerotic diseases.	Logistic regression analysis

Table 2.12: Statistical Tests for the Study Hypotheses (continued)

Study Hypotheses	Statistical Test
Goal: Evaluation of How Well Physicians Follow Lipid and Safety Monitoring Guidelines: Lipid Monitoring at Baseline	
Hypothesis 22: The likelihood of a lipid test at baseline will be higher for patients with diabetes than for those without diabetes, controlling for age, gender, ethnicity, presence of CHD, hypertension, and atherosclerotic diseases.	Logistic regression analysis
Hypothesis 23: The likelihood of a lipid test at baseline will be higher for patients with hypertension than for those without hypertension, controlling for age, gender, ethnicity, presence of CHD, diabetes, and atherosclerotic diseases.	Logistic regression analysis
Hypothesis 24: The likelihood of a lipid test at baseline will be higher for patients with atherosclerotic diseases than for those without atherosclerotic disease, controlling for age, gender, ethnicity, presence of CHD, diabetes, and hypertension.	Logistic regression analysis
Goal: Evaluation of How Well Physicians Follow Lipid and Safety Monitoring Guidelines: Lipid Monitoring After Start of Therapy	
Hypothesis 25: The likelihood of a lipid test after start of therapy will be higher for males than for females controlling for age, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.	Logistic regression analysis
Hypothesis 26: The likelihood of a lipid test after start of therapy will be higher for older patients than for younger patients, controlling for gender, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.	Logistic regression analysis
Hypothesis 27: The likelihood of a lipid test after start of therapy will be higher for non-Hispanic whites than for other ethnic groups, controlling for age, gender, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.	Logistic regression analysis

Table 2.12: Statistical Tests for the Study Hypotheses (continued)

Study Hypotheses	Statistical Test
Goal: Evaluation of How Well Physicians Follow Efficacy and Safety Monitoring Guidelines: Lipid Monitoring After Start of Therapy	
Hypothesis 28: The likelihood of a lipid test after start of therapy will be higher for patients with CHD than for those without CHD, controlling for age, gender, ethnicity, presence of diabetes, hypertension, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.	Logistic regression analysis
Hypothesis 29: The likelihood of a lipid test after start of therapy will be higher for patients with diabetes than for those without diabetes, controlling for age, gender, ethnicity, presence of CHD, hypertension, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.	Logistic regression analysis
Hypothesis 30: The likelihood of a lipid test after start of therapy will be higher for patients with hypertension than for those without hypertension, controlling for age, gender, ethnicity, presence of CHD, diabetes, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.	Logistic regression analysis
Hypothesis 31: The likelihood of a lipid test after start of therapy will be higher for patients with atherosclerotic diseases than for those without atherosclerotic diseases, controlling for age, gender, ethnicity, presence of CHD, diabetes, and hypertension, physician specialty, and lipid testing prior to index date.	Logistic regression analysis
Hypothesis 32: The likelihood of a lipid test after start of therapy will be higher for patients treated by a cardiologist at index date than those treated by other physician specialty, controlling for age, gender, ethnicity, presence of CHD, diabetes, hypertension and atherosclerotic diseases, and lipid testing prior to index date.	Logistic regression analysis
Hypothesis 33: The likelihood of a lipid test after start of therapy will be higher for patients with lipid tests at baseline than those without lipid tests at baseline, controlling for age, gender, ethnicity, presence of CHD, diabetes, and hypertension, atherosclerotic diseases, and physician specialty.	Logistic regression analysis

Table 2.12: Statistical Tests for the Study Hypotheses (continued)

Study Hypotheses	Statistical Test
Goal: Evaluation of How Well Physicians Follow Efficacy and Safety Monitoring Guidelines: Lipid Monitoring After an Initial Change in Statin Type	
Hypothesis 34: The likelihood of a lipid test after an initial change in statin type will be higher for males than for females controlling for age, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.	Logistic regression analysis
Hypothesis 35: The likelihood of a lipid test after an initial change in statin type will be higher for older patients than for younger patients, controlling for age, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.	Logistic regression analysis
Hypothesis 36: The likelihood of a lipid test after an initial change in statin type will be higher for non-Hispanic whites than for other ethnic groups, controlling for age, gender, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.	Logistic regression analysis
Hypothesis 37: The likelihood of a lipid test after an initial change in statin type will be higher for patients with CHD than for those without CHD, controlling for age, gender, ethnicity, presence of diabetes, hypertension, and atherosclerotic diseases, physician specialty and lipid testing prior to index date.	Logistic regression analysis
Hypothesis 38: The likelihood of a lipid test after an initial change in statin type will be higher for patients with diabetes than for those without diabetes, controlling for age, gender, ethnicity, presence of CHD, hypertension, and atherosclerotic diseases, physician specialty and lipid testing prior to index date.	Logistic regression analysis
Hypothesis 39: The likelihood of a lipid test after an initial change in statin type will be higher for patients with hypertension than for those without hypertension, controlling for age, gender, ethnicity, presence of CHD, diabetes, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.	Logistic regression analysis

Table 2.12: Statistical Tests for the Study Hypotheses (continued)

Study Hypotheses	Statistical Test
Goal: Evaluation of How Well Physicians Follow Efficacy and Safety Monitoring Guidelines: Lipid Monitoring After an Initial Change in Statin Type	
Hypothesis 40: The likelihood of a lipid test after an initial change in statin type will be higher for patients with atherosclerotic diseases than for those without atherosclerotic diseases, controlling for age, gender, ethnicity, presence of CHD, diabetes, and hypertension, physician specialty, and lipid testing prior to index date.	Logistic regression analysis
Hypothesis 41: The likelihood of a lipid test after an initial change in statin type will be higher for patients treated by a cardiologist at index date than those treated by other physician specialty, controlling for age, gender, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, and lipid testing prior to index date.	Logistic regression analysis
Hypothesis 42: The likelihood of a lipid test after an initial change in statin type will be higher for patients with lipid tests at baseline than those without lipid tests at baseline, controlling for age, gender, ethnicity, presence of CHD, diabetes, and hypertension, atherosclerotic diseases, and physician specialty.	Logistic regression analysis
Goal: Evaluation of How Well Physicians Follow Efficacy and Safety Monitoring Guidelines: Lipid Monitoring After an Initial Change in Statin Dose	
Hypothesis 43: The likelihood of a lipid test after an initial change in statin dose will be higher for males than for females controlling for age, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases.	Logistic regression analysis
Hypothesis 44: The likelihood of a lipid test after an initial change in statin dose will be higher for older patients than for younger patients, controlling for ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.	Logistic regression analysis
Hypothesis 45: The likelihood of a lipid test after an initial change in statin dose will be higher for non-Hispanic whites than for other ethnic groups, controlling for age, gender, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.	Logistic regression analysis

Table 2.12: Statistical Tests for the Study Hypotheses (continued)

Study Hypotheses	Statistical Test
Goal: Evaluation of How Well Physicians Follow Efficacy and Safety Monitoring Guidelines: Lipid Monitoring After an Initial Change in Statin Dose	
Hypothesis 46: The likelihood of a lipid test after an initial change in statin dose will be higher for patients with CHD than for those without CHD, controlling for age, gender, ethnicity, presence of diabetes, hypertension, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.	Logistic regression analysis
Hypothesis 47: The likelihood of a lipid test after an initial change in statin dose will be higher for patients with diabetes than for those without diabetes, controlling for age, gender, ethnicity, presence of CHD, hypertension, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.	Logistic regression analysis
Hypothesis 48: The likelihood of a lipid test after an initial change in statin dose will be higher for patients with hypertension than for those without hypertension, controlling for age, gender, ethnicity, presence of CHD, diabetes, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.	Logistic regression analysis
Hypothesis 49: The likelihood of a lipid test after an initial change in statin dose will be higher for patients with atherosclerotic diseases than for those without atherosclerotic diseases, controlling for age, gender, ethnicity, presence of CHD, diabetes, and hypertension, physician specialty and lipid testing prior to index date.	Logistic regression analysis
Hypothesis 50: The likelihood of a lipid test after an initial change in statin dose will be higher for patients treated by a cardiologist at index date than for those treated by other physician specialty, controlling for age, gender, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, and lipid testing prior to index date.	Logistic regression analysis
Hypothesis 51: The likelihood of a lipid test after an initial change in statin dose will be higher for patients with lipid tests at baseline than those without lipid tests at baseline, controlling for age, gender, ethnicity, presence of CHD, diabetes, and hypertension, atherosclerotic diseases, and physician specialty.	Logistic regression analysis

Table 2.12: Statistical Tests for the Study Hypotheses (continued)

Study Hypotheses	Statistical Test
Goal: Evaluation of How Well Physicians Follow Efficacy and Safety Monitoring Guidelines: Safety Monitoring at Baseline	
Hypothesis 52: The likelihood of an LFT at baseline will be higher for males than for females, controlling for age, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases.	Logistic regression analysis
Hypothesis 53: The likelihood of an LFT at baseline will be higher for older patients than for younger patients, controlling for gender, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases.	Logistic regression analysis
Hypothesis 54: The likelihood of an LFT at baseline will be higher for non-Hispanic whites than for other ethnic groups, controlling for age, gender, presence of CHD, diabetes, hypertension, and atherosclerotic diseases.	Logistic regression analysis
Hypothesis 55: The likelihood of an LFT at baseline will be higher for patients with CHD than for those without CHD, controlling for age, gender, ethnicity, presence of diabetes, hypertension, and atherosclerotic diseases.	Logistic regression analysis
Hypothesis 56: The likelihood of an LFT at baseline will be higher for patients with diabetes than for those without diabetes, controlling for age, gender, ethnicity, presence of CHD, hypertension, and atherosclerotic diseases.	Logistic regression analysis
Hypothesis 57: The likelihood of an LFT at baseline will be higher for patients with hypertension than for those without hypertension, controlling for age, gender, ethnicity, presence of CHD, diabetes, and atherosclerotic diseases.	Logistic regression analysis
Hypothesis 58: The likelihood of an LFT at baseline will be higher for patients with atherosclerotic diseases than those without atherosclerotic diseases, controlling for age, gender, ethnicity, presence of CHD, diabetes, and hypertension.	Logistic regression analysis

Table 2.12: Statistical Tests for the Study Hypotheses (continued)

Study Hypotheses	Statistical Test
Goal: Evaluation of How Well Physicians Follow Efficacy and Safety Monitoring Guidelines: Safety Monitoring after Start of Therapy	
Hypothesis 59: The likelihood of an LFT after start of therapy will be higher for males than for females controlling for age, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, physician specialty, and presence of LFT prior to index date.	Logistic regression analysis
Hypothesis 60: The likelihood of an LFT after start of therapy will be higher for older patients than for younger ones, controlling for gender, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, physician specialty, and presence of LFT prior to index date.	Logistic regression analysis
Hypothesis 61: The likelihood of an LFT after start of therapy will be higher for non-Hispanic whites than for other ethnic groups, controlling for age, gender, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, physician specialty and presence of LFT prior to index date.	Logistic regression analysis
Hypothesis 62: The likelihood of an LFT after start of therapy will be higher for patients with CHD than for those without CHD, controlling for age, gender, ethnicity, presence of diabetes, hypertension, and atherosclerotic diseases, physician specialty, and presence of LFT prior to index date.	Logistic regression analysis
Hypothesis 63: The likelihood of an LFT after start of therapy will be higher for patients with diabetes than for those without diabetes, controlling for age, gender, ethnicity, presence of CHD, hypertension, and atherosclerotic diseases, physician specialty, and presence of LFT prior to index date.	Logistic regression analysis
Hypothesis 64: The likelihood of an LFT after start of therapy will be higher for patients with hypertension as compared to those without hypertension, controlling for age, gender, ethnicity, presence of CHD, diabetes, and atherosclerotic diseases, physician specialty and presence of LFT prior to index date.	Logistic regression analysis

Table 2.12: Statistical Tests for the Study Hypotheses (continued)

Study Hypotheses	Statistical Test
Goal: Evaluation of How Well Physicians Follow Efficacy and Safety Monitoring Guidelines: Safety Monitoring after Start of Therapy	
Hypothesis 65: The likelihood of an LFT after start of therapy will be higher for patients with atherosclerotic diseases than for those without atherosclerotic diseases, controlling for age, gender, ethnicity, presence of CHD, diabetes, and hypertension, physician specialty, and presence of LFT prior to index date.	Logistic regression analysis
Hypothesis 66: The likelihood of an LFT after start of therapy will be higher for patients treated by a cardiologist at index date than for those treated by other physician specialty, controlling for age, gender, ethnicity, presence of CHD, diabetes, hypertension and atherosclerotic diseases, and presence of LFT prior to index date.	Logistic regression analysis
Hypothesis 67: The likelihood of an LFT after start of therapy will be higher for patients with LFTs at baseline than those without LFTs at baseline, controlling for age, gender, ethnicity, presence of CHD, diabetes, and hypertension, atherosclerotic diseases, and physician specialty.	Logistic regression analysis
Goal: Evaluation of How Well Physicians Follow Efficacy and Safety Monitoring Guidelines: Safety Monitoring after an Initial Increase in Statin Dose	
Hypothesis 68: The likelihood of an LFT after an initial increase in statin dose will be higher for males than for females controlling for age, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, physician specialty, and presence of LFT prior to index date.	Logistic regression analysis
Hypothesis 695: The likelihood of an LFT after an initial increase in statin dose will be higher for older patients than for younger patients, controlling for gender, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, physician specialty, and presence of LFT prior to index date.	Logistic regression analysis
Hypothesis 70: The likelihood of an LFT after an initial increase in statin dose will be higher for non-Hispanic whites than for ethnic groups, controlling for age, gender, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, physician specialty, and presence of LFT prior to index date.	Logistic regression analysis

Table 2.12: Statistical Tests for the Study Hypotheses (continued)

Study Hypotheses	Statistical Test
Goal: Evaluation of How Well Physicians Follow Efficacy and Safety Monitoring Guidelines: Safety Monitoring after an Initial Increase in Statin Dose	
Hypothesis 71: The likelihood of an LFT after an initial increase in statin dose will be higher for patients with CHD as compared to those without CHD, controlling for age, gender, ethnicity, presence of diabetes, hypertension, and atherosclerotic diseases, physician specialty and presence of LFT prior to index date.	Logistic regression analysis
Hypothesis 72: The likelihood of an LFT after an initial increase in statin dose will be higher for patients with diabetes as compared to those without diabetes, controlling for age, gender, ethnicity, presence of CHD, hypertension, and atherosclerotic diseases, physician specialty and presence of LFT prior to index date.	Logistic regression analysis
Hypothesis 73: The likelihood of an LFT after an initial increase in statin dose will be higher for patients with hypertension as compared to those without hypertension, controlling for age, gender, ethnicity, presence of CHD, diabetes, and atherosclerotic diseases, physician specialty, and presence of LFT prior to index date.	Logistic regression analysis
Hypothesis 74: The likelihood of an LFT after an initial increase in statin dose will be higher for patients with atherosclerotic diseases as compared to those without atherosclerotic diseases, controlling for age, gender, ethnicity, presence of CHD, diabetes, and hypertension, physician specialty, and presence of LFT prior to index date.	Logistic regression analysis
Hypothesis 75: The likelihood of an LFT after an initial increase in statin dose will be higher for patients treated by a cardiologist at index date as compared to those treated by other physician specialty, controlling for age, gender, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, and presence of LFT prior to index date.	Logistic regression analysis
Hypothesis 76: The likelihood of an LFT after start of therapy will be higher for patients with LFTs at baseline than those without LFTs at baseline, controlling for age, gender, ethnicity, presence of CHD, diabetes, and hypertension, atherosclerotic diseases, and physician specialty.	Logistic regression analysis

CHAPTER 3

RESULTS

This chapter reports the results of the data analyses. The results are presented in the order of the objectives listed in Section IX of Chapter 1. These objectives are divided in the following two sections:

1. Evaluation of statin treatment patterns and patient adherence to statin therapy; and
2. Evaluation of how well physicians follow lipid and safety monitoring guidelines.

A total of 7,440 patients met the study inclusion criteria as new statin users between the index date of September 1, 1999 and August 31, 2001 and who were continuously enrolled in the Texas Medicaid System for a year prior to the index date and two years following the index date. In addition, these patients had at least two statin prescriptions filled in a year of follow-up on two different dates. A total of 68,770 statin prescription claims were processed for 7,440 patients in a two-year follow-up period.

ANALYSES OF THE STUDY OBJECTIVES

There were 22 objectives addressing the two main goals of the study:

1. Evaluation of statin treatment patterns and patient adherence to statin therapy; and
2. Evaluation of how well physicians follow lipid and safety monitoring guidelines.

There were 12 objectives addressing the first goal, and 10 objectives addressing the second goal of the study. Objectives 1 through 10 (except objective 2) addressing the first goal of the study were exploratory in nature with no corresponding hypotheses. There was one hypothesis corresponding to study objective 2. There were 16 hypotheses corresponding to the study objectives 11 and 12, which aimed at assessing the predictors of adherence to statin therapy. There were 10 objectives assessing the second study goal. Under the second goal, objectives 16 through 22 that assessed the predictors of the occurrence of lipid and liver function tests had 59 hypotheses. In total, 76 hypotheses were tested. The study objectives that are exploratory in nature are presented first followed by analyses of the study hypotheses.

Evaluation of Statin Treatment Patterns and Patient Adherence to Statin Therapy

Objective 1: Descriptive Statistics on Statin Drug Use and Strength Prescribed at Index Date

In the present study, a majority (78.7%) of the statin users were initiated on a statin drug at the recommended starting dose. Based on the package inserts, the recommended starting doses for the statins were as follows: Lipitor® 10 or 20 mg once

daily;[420] Zocor® 20 or 40 mg once daily;[421] Pravachol® 40 mg once daily;[422] Lescol® 40 mg once daily;[423] and Mevacor® 20 mg once daily.[424] Only 94 (1.3%) were initiated on the maximum recommended dose of the statins. Overall, 40 percent of the patients were started on Lipitor® 10mg tablet, and 13.7 percent on Zocor® 20mg tablet. Table 3.1 presents information on the statin type and strength prescribed at the index date.

The most commonly prescribed statins during the two-year follow-up period were Lipitor® (57.1%), Zocor® (23.2%) and Pravachol® (14.2%). Table 3.2 provides information on the type of statin and strength based on the total number of claims for the two-year period.

Of the total 68,770 statin claims for a two-year follow-up period, 60.7 percent (N = 41,766) of the claims were for 30-days supply, 10.2 percent (N = 7,009) were for 60-days supply, and 18.4 percent (N = 12,680) for 90-days supply. Table 3.3 presents the means for quantity, number of days supply and amount paid.

[420] Lipitor package insert. Morris Plains, NJ: Parke-Davis; April 2003.
[421] Zocor package insert. West Point, PA: Merck & Co.; April 2003.
[422] Pravachol package insert. Princeton, NJ: Bristol-Myer Squibb Company. April 2003.
[423] Lescol package insert. East Hanover, NJ: Novartis Pharmaceuticals; April 2003.
[424] Mevacor package insert. West Point, PA: Merck & Co.; April 2003.

Table 3.1: Frequency and Percent of Patients Based on Statin Type and Strength Prescribed at the Index Date

Statin Type and Strength	Number of Patients	Percent
Lipitor®		
10mg	2,976	40.0%
20mg	942	12.7%
40mg	181	2.4%
80mg	11	0.1%
Total	4,110	55.2%
Zocor®		
5mg	28	0.4%
10mg	267	3.6%
20mg	1,016	13.7%
40mg	370	4.9%
80mg	59	0.8%
Total	1,740	23.4%
Pravachol®		
10mg	90	1.2%
20mg	739	9.9%
40mg	303	4.1%
Total	1,132	15.2%
Lescol®		
20mg	165	2.2%
40mg	218	2.9%
80mg XL	24	0.3%
Total	407	5.4%
Mevacor®		
10mg	12	0.2%
20mg	35	0.5%
40mg	4	0.1%
Total	51	0.8%
Total number of patients	7,440	100.0%

Table 3.2: Frequency and Percent of Total Prescription Drug Claims Based on Statin Type and Dose Prescribed to Texas Medicaid Statin Users in a Two-Year Follow-up Period

Statin Type and Strength	Number of Prescriptions	Percent of Total Prescriptions
Lipitor®		
10mg	24,965	36.3%
20mg	10,741	15.7%
40mg	3,243	4.7%
80mg	332	0.5%
Total	39,281	57.1%
Zocor®		
5mg	135	0.2%
10mg	1,991	2.9%
20mg	8,653	12.6%
40mg	4,222	6.1%
80mg	955	1.4%
Total	15,956	23.2%
Pravachol®		
10mg	691	1.0%
20mg	5,552	8.1%
40mg	3,492	5.1%
80mg	33	0.0%
Total	9,768	14.2%
Lescol®		
20mg	1,255	1.8%
40mg	218	2.4%
80mg XL	24	0.6%
Total	3,328	4.8%
Mevacor®		
10mg	92	0.1%
20mg	269	0.4%
40mg	29	0.0%
Total	390	0.5%
Lovastatin		
10mg	4	0.0%
20mg	29	0.0%
40mg	9	0.0%
Total	42	0.0%
Altocor®		
40mg	1	0.0%
60mg	4	0.0%
Total	5	0.0%
Total number of prescriptions	68,770	100.6%*

*Total percent may not equal to 100 due to rounding errors.

Table 3.3: Means, Medians and Standard Deviations for Number of Dosage Units per Claim, Number of Days Supply, and Amount Paid for Texas Medicaid Statin Prescriptions for a Two-Year Follow-up Period

	Mean (S.D.)	Median
Number of dosage units per claim	48.3 (28.0)	30.0
Number of days supply per claim	47.4 (26.3)	30.0
Dollar amount paid per claim	$122.8 (103.6)	$96.5

Objective 3: Descriptive Statistics on Lipid Lowering Drugs Prescribed Other Than Statins

Table 3.4 presents information on lipid lowering drugs other than statins that were prescribed to patients during the follow-up period. A total of 761 (10.2%) patients were prescribed other lipid-lowering drugs. A majority of the patients (N = 616; 80.9%) who received other lipid lowering agents were prescribed fibrates. Only 114 patients received a nicotinic acid derivative product.

Table 3.4: Frequency and Percent of Patients on Other Lipid-Lowering Drugs during the Two-Year Follow-up Period

Lipid Lowering Drugs	Number of Patients	Percent of Patients on Other Lipid-Lowering Drugs[a,b]	Percent of Total Patients[c]
Fibrates	616	80.9%	8.3%
Bile acid sequestrants	121	15.9%	1.6%
Nicotinic acid derivatives	114	14.9%	1.5%

[a]Calculated as a percent of 761, which is the total number of patients on other lipid-lowering drugs.
[b]Percentages do not total to 100 as some patients may be prescribed more than one class of drugs.
[c]Calculated as a percent of 7,440, which is the total number of patients in the study.

Objective 4: Specialty of the Physician Prescribing Statin at Index Date

Information on the specialty of the prescribing physician at index date was obtained from the Texas State Board of Medical Examiners (TSBME) database. The physician's unique license number was used to link the Medicaid file with the database obtained from TSBME. Overall, the specialty of index prescriber was available for 6,531 (87.8%) out of the total 7,440 patients. Family practice/general practice physicians wrote 44.6 percent of the index prescriptions (Table 3.5).

Table 3.5: Frequency and Percent at Index Date of Physician Specialty for Statin Users Aged 21-62 Years

Physician Specialty	Number of Patients	Percent of Patients
Family practice/General practice	2,916	44.6%
Internal medicine	2,108	32.3%
Cardiovascular diseases	515	7.9%
Other[a]	992	15.2%
Total[b]	6,531	100.0%

[a]Other category includes all physician specialty except family practice/general practice, internal medicine and cardiovascular diseases.
[b]Data on physician specialty were missing for 909 (12.2%) of the patients.

Objective 5: Demographic Characteristics (age, gender and ethnicity) of Statin Users

Tables 3.6 and 3.7 present demographic information of statin users. The mean age of the statin user at index date was 49.7 years (S.D. = 9.4 years) and the majority (N = 4,854; 65.2%) of the statin users were females. The age at index date ranged from 21 years to 62 years and the median age was 52 years. The frequency distribution of patients based on three age categories is as follows: 38.8 percent of the patients were between 45-55 years, 34.2 percent of the patients were between 56-62 years and 27.0 percent were between 21-44 years.

Data on ethnicity were missing for 386 patients due to omission or inappropriate coding in the Medicaid files. Of those patients for whom the data were available, the 42.7 percent of the statin users were non-Hispanic whites (N = 3,015), followed by Hispanics (N = 2,304; 32.7%) and non-Hispanic blacks (N = 1,585; 22.5%).

Table 3.6: Frequency and Percent for Gender and Mean Age at Index Date for Statin Users

Gender	Number of Patients (%)	Mean Age (S.D.) In Years	Median Age (Range) in Years
Females	4,854 (65.2%)	50.3 (8.9)	52 (21-62)
Males	2,586 (34.8%)	48.4 (9.2)	50 (21-62)
Total	7,440 (100.0%)	49.7 (9.4)	52 (21-62)

Table 3.7: Frequency and Percent of Patients Based on Ethnicity

Ethnicity	Number of Patients	Percent
White, non-Hispanic	3,015	42.7%
Hispanic	2,304	32.7%
Black, non-Hispanic	1,585	22.5%
Asian or Pacific Islander	122	1.7%
American Indian or Alaskan Native	28	0.4%
Total*	7,054	100.0%

*Data on ethnicity were missing for 386 (5.2%) of the patients due to omission or inappropriate coding in the Medicaid files.

Objective 6: Proportion of Primary and Secondary Prevention Coronary Heart Disease (CHD) Patients Started on Statin Therapy

Primary prevention patients were defined as patients without a history of established CHD, whereas secondary prevention patients were those who had a history of established CHD including indications for acute myocardial infarction, angina, chronic ischemic heart disease, history of percutaneous coronary intervention or coronary artery bypass graft. The presence for a diagnosis of CHD was determined at or a year prior to the index date.

A majority of the patients initiated on statin therapy were primary prevention patients (N = 5,597; 75.2%), i.e., they did not have a history of CHD prior to start of therapy. Of those with a diagnosis for CHD, the majority had a diagnosis for other chronic ischemic heart disease (N = 1,467; 79.6%) followed by angina (N = 848; 46.0%) (Table 3.8). Table 3.9 provides information on patients with a diagnosis for CHD, hypertension, diabetes and atherosclerotic diseases, at or a year prior to index date, and

those who presented a diagnosis for these conditions during the follow-up period. A total of 4,616 new diagnoses for hypertension, diabetes, CHD or atherosclerotic disease occurred after the index date.

Table 3.8: Frequency and Percent of Secondary Prevention CHD Patients

Types of CHD	Number of Patients	Percent[e,f]
Other chronic ischemic heart disease[a]	1,467	79.6%
Angina[b]	848	46.0%
Acute and old myocardial infarction[c]	508	27.6%
Other acute ischemic heart disease[d]	456	24.7%

[a]ICD-9 codes: 414.xx; [b]ICD-9-codes: 413, [c]ICD-9 codes: 410.33, 412; [d]ICD-9 codes: 411.xx.
[e]Percentages will not total to 100 since some patients may have more than one type of CHD.
[f]Calculated as a percent of 1,843, which is the total number of patients with a diagnosis for CHD at or a year prior to index date.

Table 3.9: Frequency and Percent of Patients with a Diagnosis for Diabetes, Hypertension, Coronary Heart Disease (CHD) and Atherosclerotic Disease at or a Year Prior to the Index Date and During Follow-up

Disease	At or Year Prior to Index Date N (%)[a,b]	Newly Diagnosed During Follow-up N (%)[a]
Hypertension	4,157 (55.9%)	1,556 (47.4%[c])
Diabetes	3,332 (44.8%)	833 (20.3%[d])
CHD	1,843 (24.8%)	1,145(20.4%[e])
Atherosclerotic Diseases	1,012 (13.6%)	1,082 (16.8%[f])
Total	7,440	4,616

[a]Percentages will not total to 100 since patients may be classified into more than one disease states.
[b]Calculated as a percent of 7,440, which is the total number of patients in the study.
[c]Calculated as a percent of 3,283, which is the number of patients with an absence of a diagnosis for hypertension at or a year prior to the index date.
[d]Calculated as a percent of 4,108, which is the number of patients with an absence of a diagnosis for diabetes at or a year prior to the index date.
[e]Calculated as a percent of 5,597, which is the number of patients with an absence of a diagnosis for CHD at or a year prior to the index date.
[f]Calculated as a percent of 6,428, which is the number of patients with an absence of a diagnosis for atherosclerotic diseases at or a year prior to the index date.

Objective 7: Number and Type of CHD Risk Factors

The frequency and percent of patients based on the number and types of risk factors were assessed a year prior to or at index date. The results are presented in Tables 3.10 and 3.11. The risk factors for CHD that were assessed included age and gender (males > 45 years or females > 55 years), presence of a diagnosis for diabetes or hypertension or both. The mean number of CHD risk factor per patient was 1.5 (S.D. = 0.9). A total of 48.7 percent (N = 3,625) of the patients had two or more CHD risk factors.

Table 3.10: Frequency and Percent of Patients by the Number of Risk Factors for CHD a Year Prior or At Index Date

Number of Risk Factors*	Number of Patients	Percent
0	1,358	18.3%
1	2,457	33.0%
2	2,428	32.6%
3	1,197	16.1%
Total	7,440	100.0%

*Calculated based on the presence of one or more of the following risk factors: diabetes, hypertension, age and gender (males > 45 years or females > 55 years).

Table 3.11: Frequency and Percent of Patients by the Type of Risk Factors

Type of Risk Factors	Number of Patients with Risk Factors	Percent of Patients[a,b]
Hypertension	4,157	55.9%
Age and Gender (males > 45 years or females > 55 years)	3,416	45.9%
Females > 55 years	1,732	
Males > 45 years	1,684	
Diabetes	3,332	44.8%

[a]Calculated as a percent of 7,440, which is the total number of patients in the study.
[b]Percent will not total to 100 since patients could have more than one of the above risk factors.

Objective 8: Patient Adherence to Statin Therapy Based on Prescription Refill Records

Adherence to statin therapy was assessed by calculating the medication possession ratio (MPR). The MPR was calculated using the following formula:

$$\text{MPR} = \frac{\text{Sum of days supply dispensed (except supply at last refill date)}}{\text{Sum of days between the first and the last prescription refill dates}}$$

The mean MPR was 0.7 (S.D. = 0.2). The median MPR was 0.74 and the MPR ranged from 0.08 to 2.00. Table 3.12 presents the distribution of MPR into four categories (0.08 – 0.40; 0.41 – 0.79; 0.80 – 1.0; 1.01 – 2.0) and the number of patients in each category. Over half of the patients (N = 4,222; 56.7%) had an MPR of less than 0.80. Table 3.13 presents the MPR controlling for gender and ethnicity.

An independent samples t-test was conducted to assess the difference in MPR with respect to gender. The mean MPR for males was found to be statistically different from females (0.73 vs. 0.68) (t –statistic = -6.596; df = 7438; $p < 0.001$). However, the difference was just 0.05 which may not be practically different.

A one-way analysis of variance was used to assess the differences in MPR with respect to ethnicity. Overall, the MPR differed significantly with respect to ethnicity ($F(4, 7049) = 40.7$; $p < 0.001$). Post-hoc comparisons using Bonferroni correction revealed significant differences in the mean MPR between non-Hispanic whites and non-Hispanic blacks (0.75 vs. 0.66; $p < 0.001$), and between non-Hispanic whites and Hispanics (0.75 vs. 0.67; $p < 0.001$). Though significant statistically, the MPR did not differ substantially

with respect to gender and ethnicity, and the statistical significance could be attributed to the large sample size.

Table 3.12: Frequency and Percent of Patients Based on Categories of Medication Possession Ratio (MPR)

MPR Category	Number of Patients	Percent
0.08 through 0.40	1,320	17.7%
0.41 through 0.79	2,902	39.0%
0.80 through 1.00	2,355	31.7%
1.01 through 2.00	863	11.6%
Total	7,440	100.0%

Table 3.13: Mean Medication Possession Ratio for Statin Therapy Controlling for Gender and Ethnicity

Demographic Characteristic	Mean MPR (S.D.)
Gender	
Male	0.73 (0.28)[a]
Female	0.68 (0.28)[a]
Ethnicity[b]	
White, non-Hispanic	0.75 (0.27)[c,d]
Hispanic	0.67 (0.28)[c]
Black, non-Hispanic	0.66 (0.28)[d]
American Indian or Alaskan	0.74 (0.32)
Asian or Pacific Islander	0.72 (0.30)

Matched letters indicate statistical difference

[a]Mean difference = 0.04511; t-statistic = -6.596; df = 7,438; $p < 0.001$.

[b]$F(4,7049) = 40.670$; $p < 0.001$.

[c]Mean difference = 0.0817; $p < 0.001$.

[d]Mean difference = 0.0913; $p < 0.001$.

Objective 9: Persistence to Statin Therapy

Persistence to statin drug therapy was expressed as the number of days on statin therapy before the patient discontinued the therapy. Discontinuation was defined as failure to refill the prescription within 60 days of exhausting the last supply. Thus, if the patient had greater than 60 days between the calculated last day of therapy and the date of the next refill, then the patient was categorized as discontinuing therapy. Obviously, if there was no refill, then the patient was classified as discontinuing therapy. A sensitivity analysis was conducted using a gap of 45 days. Kaplan Meier survival estimate was conducted to show a graphical representation of the proportion of patients persistent with statins. The results of the Kaplan Meier survival analysis are presented based on the 60 - day gap (Figure 3.1) and on the 45-day gap (Figure 3.2) of failure to refill the statin prescription.

Sixty-Days Gap

Based on a 60-day gap of failing to refill the prescription, the mean days of persistency to statin therapy was 381 days (95% CI: 374.0-389.0) or just over a year. The days of persistence for 17.8 percent of the patients (N = 1,327) was zero, implying that these patients exceeded the 60-days gap for their first statin prescription refill. Only 50 percent (N = 3,720) of the patients were persistent with their statin therapy at the end of 310 days. The probability of being persistent at the end of the two year follow-up period was 0.41 (Figure 3.1).

Forty-five Day Gap

Based on a 45-day gap of failing to refill the prescription, the mean days of persistency to statin therapy was 329 days (95% CI: 321.8-336.5). The days of persistence for 21.8 percent of the patients (N = 1,620) was zero, implying that these patients exceeded the 45-day gap for their first statin prescription refill. Only 50 percent (N = 3,720) of the patients were persistent with their statin therapy at the end of 206 days. The probability of being persistent at the end of the two year follow-up period was 0.33 (Figure 3.2).

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Figure 3.1: Kaplan-Meier Survival Estimate of Persistence to Statin Therapy for a Two-Year Follow-Up Period with a Gap of Sixty Days of Failure to Refill Statin Prescription

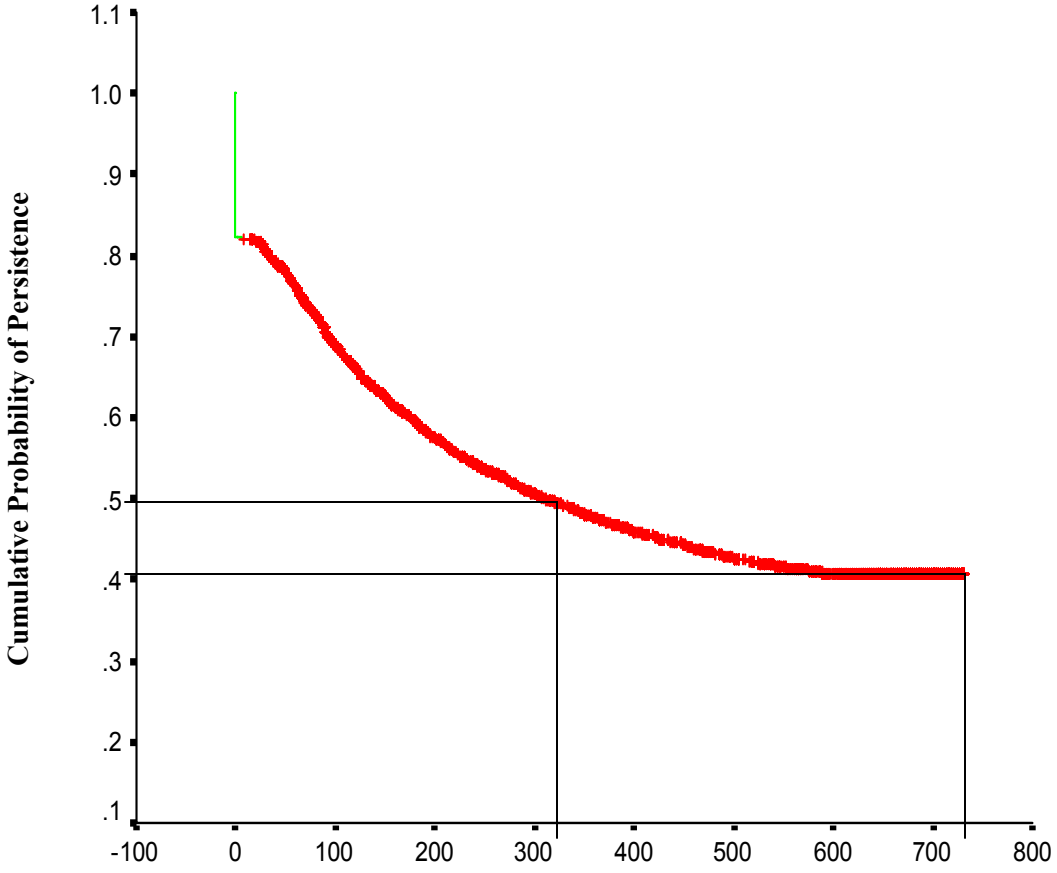
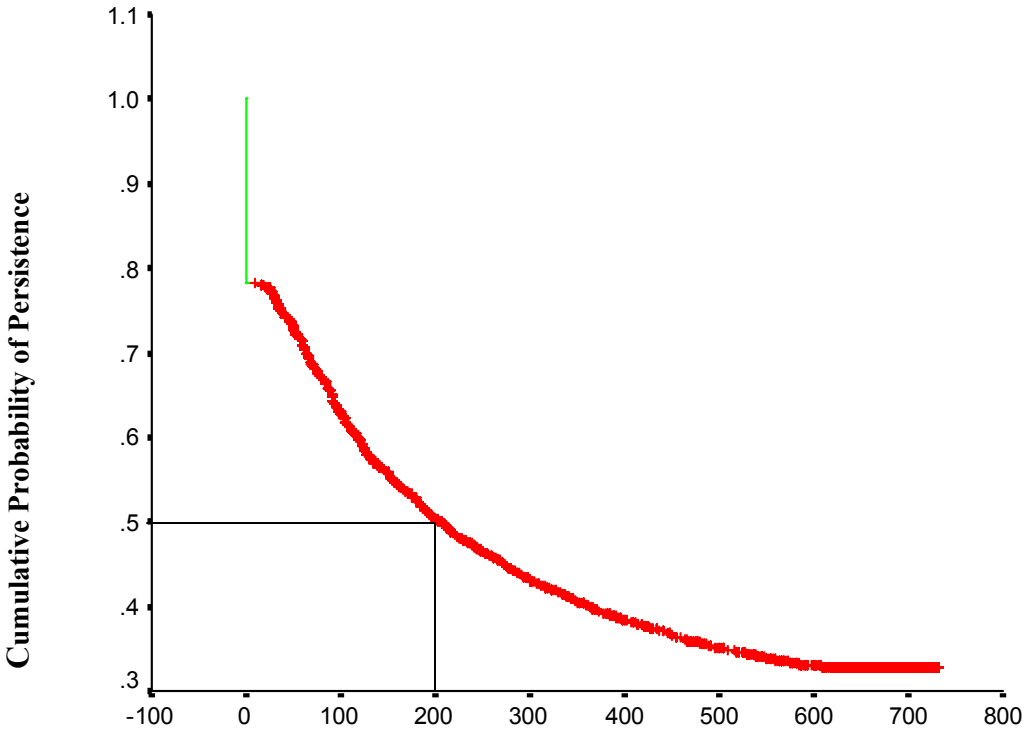


Figure 3.2: Kaplan-Meier Survival Estimate of Persistence to Statin Therapy for a Two-Year Follow-Up Period with a Gap of Forty-Five Days of Failure to Refill Statin Prescription



Objective 10: Amount Reimbursed by Medicaid for Statin Drugs

In the analysis determining the total amount Texas Medicaid paid for statin drugs it was decided to sum the total amount spent on each patient for the two-year follow-up period. This calculation would give us the total amount spent per patient by Medicaid for the two-year follow-up period. The mean of the amount spent was $1,116.80 (S.D. = $729.38) and the median was $1,021.34. The amount ranged from a minimum of $38.70 to a maximum of $8,114.24. Outliers on the cost data were detected with the help of Z-scores. Those scores in the excess of 3.3 are considered as potential outliers.[425]

There were 20 cases with Z-scores above 3.3; these cases were examined. The extreme values on the cost data (above $3,540.18) was due to large quantities of statin drugs dispensed, thus a decision was made to retain them in the analysis. However, only one case was deleted from the analysis because the total amount reimbursed for the two-year period was unusually high ($8,114.24). Thus, the amount reimbursed by Medicaid for statin drugs was calculated for 7,439 patients. The total dollar amount reimbursed by Medicaid for statin drugs, for the two-year follow-up period, for 7,439 patients in the study, was $8.3 million. The amount reimbursed ranged from a minimum of $38.70 to a maximum amount of $5,108.50. The median cost reimbursed by Medicaid was $1,021.34 and the mean cost was $1,116.80 (S.D = $729.38). Per member per month cost to Medicaid for statin drugs was $46.50.

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[425] Tabachnick BG, Fidell LS. Cleaning up your act: screening data prior to analysis. *Using Multivariate Statistics*. Fourth ed. Boston: Allyn and Bacon; 2001:56-107.

Objective 11 and 12: Factors Affecting Adherence and Persistence to Statin Therapy

Study objectives 11 and 12, which aimed at determining the factors that are related to adherence and persistence to statin therapy, respectively, will be addressed in the section that tests the study hypotheses, later in this chapter.

Evaluation of How Well Physicians Follow Lipid and Safety Monitoring Guidelines

Objective 13: Monitoring of Lipid Levels

The ATP II guidelines recommend LDL monitoring prior to initiating drug therapy as well as follow-up measurements. Based on the guidelines, it is important to have a minimum of two lipoprotein measurements during one to two months of diet therapy prior to initiating the drug therapy. After starting drug therapy, the first lipoprotein measurement is recommended at six to eight weeks. Once the target LDL levels are reached, patients should be monitored every eight to twelve week intervals through 52 weeks. After a year of therapy, once the LDL levels are attained, monitoring of lipids and adverse effects should be conducted at four- to six-month intervals. In addition, the ATP III guidelines recommend lipid monitoring within six to eight weeks following a change in drug regimen.[426]

To determine the extent physicians monitor patients' lipid levels as per the guidelines, the monitoring of low-density lipoproteins (LDL) was assessed at baseline

[426] Grundy SM, Becker DM, Clark L, et al. Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *Journal of the American Medical Association.* 2001;285(19):2486-2497.

(within three months prior to index date), within three-months (but not earlier than six weeks) after the index date and six-months thereafter. The presence of procedural codes for lipid tests in the medical claims file of Texas Medicaid were used to assess monitoring of lipid levels. Table 3.14 presents the results.

Within three months prior to the start of therapy, 42.5 percent (N = 3,163) of the total patients had their LDL levels monitored. A majority of the patients (N = 6,282; 84.4%) did not have a follow-up lipid test within three months since the start of therapy. Of those patients who had their lipid levels monitored within three months since the start of therapy (N = 1,158), only 67 patients (5.8%) had lipid monitoring within six months thereafter. Thus, out of the total patients in the study (N = 7,440), only 0.9 percent of the patients (N = 67) had their LDL levels monitored as per the guidelines.

In addition, LDL monitoring was assessed in patients who were persistent to statin therapy for three months or more. A total of 4,888 (65.7%) were persistent to therapy for three months or more. Of these only 43.8 percent (N = 2,118) had baseline lipid tests. Only 16.5 percent (N = 808) had LDL tests within three months after the start of therapy. Only 0.8 percent (N = 40) had LDL levels tested at three months after the start of therapy and six months thereafter.

Monitoring of LDL levels was also assessed among patients who were persistent to therapy for six months or more. A total of 3,786 (50.8%) were persistent to therapy for six months or more. Of these only 42.4 percent (N = 1,605) had baseline lipid tests. Only 16.3 percent (N = 616) had LDL tests within three months after the start of therapy. Only

0.7 percent (N = 27) had LDL levels tested at three months after the start of therapy and six months thereafter.

LDL monitoring within six months and a year prior to the start of therapy were also assessed. Table 3.15 presents these results. Six months before the start of therapy, 49.6 percent (N = 3,694) of the patients had their LDL levels monitored, whereas within a year following the start of therapy, 49.9 percent (N = 3,717) of the total patients had their LDL levels measured.

Table 3.14: Frequency and Percent of Statin Users with LDL Monitoring at Baseline, Within Three Months from Start of Statin Therapy and Six Months Thereafter

Interval	LDL Monitoring	
	Number of Patients	Percent
Baseline (three months prior to start of therapy)[a]	3,163	42.5%
Test within three months (but not earlier than six weeks) after start of therapy[a]	1,158	15.6%
Test within three months after start of therapy (but not earlier than six weeks) **and** within six months thereafter[b]	67	0.9%[a] 5.8%[b]

[a]Calculated as a percent of 7,440 which is the total number of patients started on statin therapy.
[b]Calculated as a percent of 1,158 which is the total number of patients who had a test within three months after start of therapy.

Table 3.15: Frequency and Percent of Patients with LDL Monitoring Six Months and A Year Prior to and After the Start of Statin Therapy

Interval	LDL Monitoring	
	Number of Patients	Percent*
Prior to start of therapy		
Six months	3,694	49.6%
One year	4,174	56.1%
After start of therapy		
Six months	2,497	33.5%
One year	3,717	49.9%

*Calculated as a percent of 7,440 which is the total number of patients initiated on statin therapy.

The guidelines also recommend LDL monitoring within three months (but not earlier than six weeks) of a change in dose or change in statin drug. Table 3.16 presents the results for only LDL monitoring following the first time there was a change in statin type or dose. A total of 2,160 patients had a change in statin dose and a total of 1,263 patients had a change in a statin drug type for the first time since the start of therapy. Following a change in therapy, LDL monitoring was low, with only 15.5 (N = 335) and 14.1 percent (N = 178) of the patients having their LDL levels monitored within three months following a change in statin type or dose, respectively.

Table 3.16: Frequency and Percent of Statin Users with LDL Monitoring Following a Change in Statin Type or Dose for the First Time Since Start of Therapy

Interval	LDL Monitoring	
	Number of Patients	Percent
Within three months following a change in dose[a]	335	15.5%
Within three months following change in statin type[b]	178	14.1%

[a]Percent calculated from a total of 2,160 statin users who had an initial change in statin dose.
[b]Percent calculated from a total of 1,263 statin users who had an initial change in statin type.

There may be many reasons for a change in drug therapy. It may be due to poor performance of the drug or may be due to side effects of the drug. For those patients who had a change, the proportion of the patients with LDL monitoring three months prior to the change was determined. Table 3.17 presents the results of this analysis.

Table 3.17: Frequency and Percent of Patients with LDL Monitoring Three Months Prior to an Initial Change in Statin Dose or Type

Interval	LDL Monitoring	
	Number of Patients	Percent
Three months prior to an initial change in dose[a]	889	41.2%
Three months prior to an initial change in statin type[b]	491	38.9%

[a]Percent calculated from a total of 2,160 statin users who had an initial change in statin dose.
[b]Percent calculated from a total of 1,263 statin users who had an initial change in statin type.

The differences in lipid monitoring with respect to physician characteristics such as age, gender and years of licensure for the physician were also evaluated. The number of tests based on the proportion of patients seen by a physician was calculated. For example, if a physician saw three patients and of these three patients, the tests were conducted in only one patient then the proportion of tests conducted will be 0.33 for that physician. Based on the frequency distribution, it was observed that most of the cases were concentrated where the proportions were either zero or one. Hence, for the purpose of statistical analysis, only those cases where the proportions were zero or one were included.

A chi-square analysis was conducted to assess if there was an association between the proportion of tests per physician at baseline (three months prior to index date) and follow-up (within three months from the start of therapy) and physician's gender. No significant association was observed between the proportion of lipid tests at baseline (Chi-square = 1.070; df = 1; p = 0.301) and follow-up (Chi-square = 0.004; df = 1; p = 0.406) and physician's gender.

A Pearson's correlation was used to assess the relationship between the proportion of lipid tests at baseline and follow-up and physician's age and the years of licensure. No significant correlation was observed between the age of the physician and the proportion of lipid tests at baseline ($r = -0.007$; $p = 0.74$) and follow-up ($r = -0.003$; $p = 0.9$). Similarly, no significant correlation was observed between the year of licensure and the proportion of lipid tests at baseline ($r = -0.25$; $p = 0.216$) and follow-up ($r = 0.005$; $p = 0.789$).

Objective 14: Monitoring of Liver Function

Adverse events associated with the use of statins include abnormalities in liver function and the occurrence of rhabdomylosis or muscle pain. Thus, the guidelines call for conducting liver function tests (LFTs) to assess the side effects of statins before and after the start of therapy and following an increase in statin dose. Presence of liver function tests (LFTs) was assessed to evaluate monitoring for adverse drug events associated with the use of statin drugs. Presence of LFTs was assessed from the procedural codes in the Texas Medicaid Medical Claims file. LFTs were assessed at baseline (three months prior to index date), within three months (but not earlier than six weeks) after the index date and six months thereafter. Table 3.18 presents the results.

Within three months prior to the start of therapy, only 14.7 percent (N = 1,099) of the total patients had LFTs. Only, 9.7 percent (N = 724) of the patients had an LFT within three months since the start of therapy. Of those patients who had their liver

function monitored within three months since the start of therapy (N = 724), only 35 patients (4.8%) had LFTs within six months thereafter.

Table 3.19 presents the results of the presence of LFTs within six months and a year prior to the start of therapy. A greater number of patients had LFTs within a year as compared to three months since the start of therapy (31.6% vs. 9.7%).

Table 3.18: Frequency and Percent of Statin Users with Liver Function Tests (LFTs) at Baseline, Within Three Months from Start of Statin Therapy and Six Months Thereafter

Interval	Liver Function Tests	
	Number of Patients	Percent
Baseline (three months prior to start of therapy)[a]	1,099	14.7%
Test within three months (but not earlier than six weeks) after start of therapy [a]	724	9.7%
Test within three months after start of therapy (but not earlier than six weeks) and within six months thereafter[b]	35	0.5%[a] 4.8%[b]

[a]Calculated as a percent of 7,440 which is the total number of patients started on statin therapy.
[b]Calculated as a percent of 724 which is the total number of patients who had a LFT within three months after start of therapy.

Table 3.19: Frequency and Percent of Patients with Liver Function Tests (LFTs) Six Months and a Year Prior to and After the Start of Statin Therapy

Interval	LFTs Conducted	
	Number of Patients	Percent*
Prior to start of therapy		
Six months	1,518	20.4%
One year	2,016	27.1%
After start of therapy		
Six months	1,496	20.1%
One year	2,350	31.6%

*Calculated as a percent of 7,440 which is the total number of patients initiated on statin therapy.

The differences in LFTs with respect to physician characteristics such as age, gender and years of licensure for the physician were also evaluated. The number of tests based on the proportion of patients seen by a physician was calculated. For example, if a physician saw three patients and of these three patients, the tests were conducted in only one patient, then the proportion of tests conducted will be 0.33 for that physician. Based on the frequency distribution, it was observed that most of the cases were concentrated where the proportions were either zero or one. Hence, for the purpose of statistical analysis, only cases where the proportions were zero or one were included.

A chi-square analysis was conducted to assess if there was an association between the proportion of tests per physician at baseline (three months prior to index date) and follow-up (within three months from the start of therapy) and physician's gender. No significant association was observed between the proportion of LFTs as baseline (Chi-

square = 0.690; df = 1; p = 0.406) and follow-up (Chi-square = 0.027; df = 1; p = 0.869) and physician's gender.

A Pearson's correlation was used to assess the relationship between the proportion of LFTs tests at baseline and follow-up and physician's age and the years of licensure. No significant correlation was observed between the age of the physician and the proportion of LFTs at baseline (r = -0.040; p = 0.073) and follow-up (r = -0.031; p = 0.168). Similarly, no significant correlation was observed between the year of licensure and the proportion of LFTs at baseline (r = -0.038; p = 0.62) and follow-up (r = -0.013; p = 0.534).

Objective 15: Monitoring of Liver Function Following an Increase in Statin Dose

A total of 2,352 statin users had an increase in statin dose for the first time following the start of therapy. Of these, 1,896 had an increase in dose of their initial statin and 456 had a change in statin type along with an increase in dose. Presence of LFTs within three months (but not earlier than six weeks) was assessed following the increase in dose. Only 7.9 percent (N = 185) of the total patients who had an initial increase in statin dose had an LFT within three months following the dose increase.

Objectives 16 through 22: Predictors of Lipid and Liver Function Monitoring

Objectives 16 through 22 that aimed at assessing the predictors of the occurrence of lipid monitoring and liver function monitoring are addressed in the analyses of study hypotheses section which follows.

Testing of Study Hypotheses Related to the Objectives

The study hypotheses that are tested relate to the following objectives:

Objective 2

To determine the association between statin dose prescribed at index date and CHD status at or prior to the index date.

Objective 11

To determine if factors such as demographic characteristics (age, gender and ethnicity), type of CHD prevention, presence of diabetes, hypertension, and atherosclerotic diseases, and total number of prescriptions are predictors of adherence to statin therapy.

Objective 12

To determine if factors such as demographic characteristics (age, gender and ethnicity), type of CHD prevention, presence of diabetes, hypertension, and atherosclerotic diseases, and total number of prescriptions are predictors of persistence to statin therapy.

Objective 16

To determine if factors such as demographic characteristics (age, gender and ethnicity), type of CHD prevention, presence of diabetes, hypertension, and atherosclerotic disease,

are predictors of the occurrence of lipid monitoring tests at baseline (within three months prior to start of therapy).

Objective 17

To determine if factors such as demographic characteristics (age, gender and ethnicity), type of CHD prevention, presence of diabetes, hypertension, and atherosclerotic disease, physician specialty at index date and lipid testing at baseline are predictors of the occurrence of lipid monitoring after the start of therapy (within three months, but not earlier than six weeks since the start of therapy).

Objective 18

To determine if factors such as demographic characteristics (age, gender and ethnicity), type of CHD prevention, presence of diabetes, hypertension, and atherosclerotic disease, physician specialty at index date and lipid testing at baseline are predictors of the occurrence of lipid monitoring (within three months, but not earlier than six weeks) following the initial change in statin type.

Objective 19

To determine if factors such as demographic characteristics (age, gender and ethnicity), type of CHD prevention, presence of diabetes, hypertension, and atherosclerotic disease, physician specialty at index date and lipid testing at baseline are predictors of the occurrence of lipid monitoring (within three months, but not earlier than six weeks) following the initial change in statin dose.

Objective 20

To determine if factors such as demographic characteristics (age, gender and ethnicity), type of CHD prevention, presence of diabetes, hypertension, and atherosclerotic disease, are predictors of the occurrence of LFTs at baseline (within three months prior to start of therapy).

Objective 21

To determine if factors such as demographic characteristics (age, gender and ethnicity), type of CHD prevention, presence of diabetes, hypertension, and atherosclerotic disease, physician specialty at index date and LFTs at baseline are predictors of the occurrence of LFTs (within three months, but not earlier than six weeks) after the start of therapy.

Objective 22

To determine if factors such as demographic characteristics (age, gender and ethnicity), type of CHD prevention, presence of diabetes, hypertension, and atherosclerotic disease, physician specialty at index date and LFTs at baseline are predictors of the occurrence of LFTs (within three months, but not earlier than six weeks) following the initial increase in statin dose.

The following statistical tools were used to address the study hypotheses:

1. Chi-square analysis;
2. Multiple regression;
3. Cox proportional hazards model;
4. Logistic regression.

An *a priori* alpha level of 0.05 was used to test the study hypotheses. The evaluation of assumptions related to the statistical tests is presented.

Assessment of Missing Data and Outliers for the Independent Variables

For the above analyses, the data were screened for any missing values and outliers. There were no missing values on any of the independent variables except for ethnicity and physician specialty, where 5.1 percent (386/7440) and 12.2 percent (909/7440) of the data were missing, respectively. The missing cases on these variables were deleted from further analyses.

Outliers for continuous predictor variables were evaluated using methods proposed by Tabachnick and Fidell.[427] Z-scores were used to assess univariate outliers for the continuous variables such as age and the total number of prescriptions, used in the regression models. Those cases with z-scores in excess of 3.3 were considered as outliers and were deleted from the dataset. No outliers were detected for the variable age. Univariate outliers were detected for the total of number of prescriptions (Mean = 15.70; S.D. = 10.2; Minimum = 1; Maximum = 86) over the two-year follow-up period; and those cases with greater than 50 prescriptions (94 cases) were deleted from further analyses.

[427] Tabachnick BG, Fidell LS. Cleaning up your act: screening data prior to analysis. *Using Multivariate Statistics*. Fourth ed. Boston: Allyn and Bacon; 2001:56-107.

Testing of Assumptions

The statistical tests that were used to test the study hypotheses included multiple regression, logistic regression and Cox proportional hazards model. The assumptions with regards to each of these analyses were evaluated and presented in the following sections.

Evaluation of Assumptions of Logistic Regression

Although logistic regression makes no assumption of the distribution of the predictor variables, assumptions of sampling adequacy, multicollinearity, linearity of the logits and omission of outliers are critical to logistic regression.[428] These assumptions were tested as a part of the analysis. The assumption testing applies for all seven logistic regression models.

Since the goodness-of-fit test in logistic regression compares the observed with expected frequencies in cells formed by the variables, the analysis may lack power if the cell counts are too small. Thus, it is important to evaluate the expected cell frequencies for all pairs of variables including the outcome variables. The requirement of sampling adequacy is that no cell should have expected frequencies less than one and no more than 20 percent of the cells should have expected frequencies of less than five. This assumption was violated in three models that assessed predictors of lipid monitoring following a dose and drug change, and liver function monitoring following a dose

[428] Tabachnick BG, Fidell LS. Logistic regression. *Using Multivariate Statistics*. Fourth ed. Boston: Allyn and Bacon; 2001:517-581.

increase. This was caused by small cell size for the ethnicity categories of Asian or Pacific Islanders and American Indians or Alaskans. In order to increase the size of the expected frequencies, Hosmer and Lemeshow recommend collapsing the categories.[429] Based on this recommendation, these two categories for ethnicity were collapsed into one to satisfy the assumption. The collapsed category was titled "American Indian or Alaskan/Asian or Pacific Islander and consisted of 40 subjects in the analysis assessing the presence of lipid tests and LFTs following a dose increase and 32 subjects in the analysis assessing the presence of lipid test following a change in statin type.

Logistic regression is sensitive to very high correlation among the predictor variables. Very high correlations can be detected by high standard errors for the parameter estimates as well as failure of the model to converge. However, there was no problem with model convergence and the standard errors of the parameters were not very large, therefore, multicollinearity was not an issue in any of the models. The logistic regression results are tabulated later in the chapter.

Although there are no linearity assumptions among the predictor variables in logistic regression, there exists an assumption of linearity between the continuous predictor variables and the logit transformation of the outcome variables. Linearity of the logits among the predictors variables was assessed using the Box-Tidwell transformation of the continuous predictor variables (i.e., age) as proposed by Hosmer and Lemeshow.[430]

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[429] Hosmer DW, Lemeshow S. Assessing the fit of the model. *Applied Logistic Regression*. New York: John Wiley & Sons; 1989:135-173.
[430] Tabachnick BG, Fidell LS. Model building strategies and methods for logistic regression. *Applied Logistic Regression*. New York: John Wiley & Sons; 1989:82-133.

In the Box-Tidwell transformation, the interactions between each predictor and its natural logarithm are added to the logistic regression model. There is a violation of the assumption if the interactions are significant. Since the added interaction term was not statistically significant, this assumption was not violated. No multivariate outliers were detected the in any of the regression solutions, hence presence of multivariate outliers was not an issue.

Evaluation of Assumption for Cox Regression Analysis

The proportionality of hazards assumption was evaluated. The proportionality of hazards assumption is that the "shapes of the survival functions are the same for all groups over time." This implies that the failure rates across all groups are the same even if the "time to event" is different. If the survival functions for different groups appear to be parallel this assumption is met.[431,432] The survival curves were observed for each level of the predictor variables and the lines appeared parallel thus satisfying the assumption of proportionality of hazards (Appendix A).

[431] Tabachnick BG, Fidell LS. Survival/failure analysis. *Using Multivariate Statistics*. Fourth ed. Boston: Allyn and Bacon; 2001:772-836.
[432] Allison PD. Estimating Cox regression models with PROC PHREG. *Survival Analysis Using the SAS Sytem: A Practical Guide*. Cary, NC: SAS Institute Inc.; 1995:111-184.

Evaluation of Assumptions for Multiple Regression

The following assumptions for multiple regression were tested: absence of multicollinearity, normality, linearity and homoscedasticity of the residuals, independence of the error terms, and absence of outliers in the regression solution.

Multicollinearity in regression models are high levels of intercorrelation among the predictor variables such that the effects of the variables cannot be separated. Tabachnick and Fidell indicate that a correlation of 0.90 or higher between the predictor variables would be a cause for concern.[433] Multicollinearity will be detected with the variance proportions and the tolerance values of the variables. Variables with large variance proportions (i.e., greater than 0.5 on at least two variables for a given dimension) would present a collinearity problem. Multicollinearity may be present if the tolerance for each of the independent variables is small (less than 0.1) since this would indicate that the variable is "almost a linear combination of other independent variables."[434] There was a lack of multicollinearity among the independent variables as the variance proportions were lower than 0.5 and none of the variables had a tolerance value of less than 0.1.

The assumptions of normality, linearity and homoscedascticity of the residuals were assessed by examining the residual scatterplots. The plots of standardized residuals

[433] Tabachnick BG, Fidell LS. Cleaning up your act: screening data prior to analysis. *Using Multivariate Statistics*. Fourth ed. Boston: Allyn and Bacon; 2001:56-107.
[434] Norusis MJ. Building multiple regression models. *SPSS 10.0 Guide to Data Analysis*. New Jersey: Prentice-Hall; 2000:455-482.

against the standardized estimates of the dependent variable (mean MPR) showed that the assumptions of normality, linearity, and homoscedascticity were satisfied.

Another assumption of regression, that errors of prediction are independent of one another, was evaluated with the help of Durbin-Watson coefficient. Durbin-Watson statistic is a "measure of autocorrelation of errors over the sequence of cases."[435] As a rule of thumb, the value of the coefficient between 1.5 and 2.5 indicates uncorrelated error terms. A Durbin-Watson statistic of 1.804 was obtained for the model, thus the error terms were independent.

Multivariate outliers were assessed and cases with extreme values were detected by measuring the Cook's distance, where values greater than one indicate presence of multicollinearity. Cook's distance measures the change in the regression coefficients as a result of elimination of a case from the analysis.[436] In the analysis, very small values ranging from zero to 0.014 were obtained for the Cook's distance indicating absence of multivariate outliers.

Evaluation of Statin Treatment Patterns and Patient Adherence to Statin Therapy

This objective tests the hypotheses related to assessing the differences in starting dose between primary and secondary prevention patients and assessing predictors of adherence to therapy. Independent samples t-test, multiple regression, and Cox

[435] Tabachnick BG, Fidell LS. Multiple regression. *Using Multivariate Statistics*. Fourth ed. Boston: Allyn and Bacon; 2001:111-176.
[436] Norusis MJ. Multiple regression diagnostics. *SPSS 10.0 Guide to Data Analysis*. New Jersey: Prentice-Hall; 2000:489-503.

regression were used to address the hypotheses. The study objectives as well as the corresponding hypotheses will be restated along with the statistical analysis utilized.

Objective 2: To determine the association between statin dose prescribed at index date and CHD status at or prior to the index date.

Hypothesis 1: The starting dose for statin therapy for secondary prevention patients will be higher than for primary prevention patients, controlling for the type of statin.

A chi-square analysis was conducted to assess the association between the starting dose and CHD status, by statin type for the top three statins (Lipitor®, Zocor® and Pravachol®). The patients on the top three statins represented 93.8 percent (N = 6,982) of the total patients. A significant association was observed between the starting dose and CHD status for patients on Lipitor® (Chi-square = 36.016; df = 3; $p < 0.001$). Table 3.20 presents the frequency and proportion of patients with and without CHD, by the starting dose of Lipitor®. For patients started on Lipitor®, 24.2 percent (N = 994) had CHD and 75.8 percent did not have CHD (N = 3,116). A chi-square analysis did not yield a significant association between the starting dose and CHD status for those patients on Zocor® (Chi-square = 7.398; df = 4; $p = 0.116$) or Pravachol® (Chi-square = 2.981; df = 2; $p = 0.225$). Based on the results hypothesis 1 was rejected.

Table 3.20: Frequency and Proportion of Patients with CHD and without CHD by Starting Dose of Lipitor®

	Statin Type and Strength				Row Total (%)
	Lipitor® 10mg	**Lipitor® 20mg**	**Lipitor® 40mg**	**Lipitor® 80mg**	
Non-CHD	2299	705	105	7	3116 (75.8%)
CHD	677	237	76	4	994 (24.2%)
Column Total (%)	2976 (72.4%)	942 (22.9%)	181 (4.4%)	11 (0.3%)	4110 (100.0%)

Chi-square = 36.016; df = 3; $p < 0.001$

Objective 11: To determine if factors such as demographic characteristics (age, gender and ethnicity), type of CHD prevention, presence of diabetes, hypertension, and atherosclerotic diseases, and total number of other prescriptions are predictors of adherence to statin therapy.

Study objective 11, which is represented by hypotheses 2 through 9, was assessed using multiple regression analysis. The dependent variable, MPR was calculated for each patient and regression analysis was employed. The calculated MPR (mean = 0.70, S.D. = 0.28) had a normal distribution. The predictor variables included in the model were patient's age at index date, gender, ethnicity, presence of CHD, diabetes, hypertension, atherosclerotic disease, and total number of prescriptions other than lipid-lowering drugs during the two-year follow-up. The multiple regression equation is as follows:

$Y = \alpha + \beta_1$ age $+ \beta_2$ gender $+ \beta_3$ ethnicity $+ \beta_4$ CHD $+ \beta_5$ diabetes $+ \beta_6$ hypertension $+ \beta_7$ atherosclerotic disease $+ \beta_8$ total number of prescriptions $+ \varepsilon$

where Y = predicted value of the MPR

β_i (i=1,2,3,4,5,6,7,8)= coefficient for the change in the predicted value of MPR associated with a one unit change in gender, ethnicity, type of CHD prevention, presence of diabetes as a risk factor, presence of hypertension as a risk factor, presence of atherosclerotic disease and total number of prescriptions.

ε = error term

In multiple regression analysis, the independent variables have to be either continuous or dummy coded dichotomous variables. Some of the independent variables such as ethnicity and disease conditions (CHD, diabetes, hypertension or atherosclerotic diseases) in the model were discrete variables, having more than two categories. These variables had to be dummy coded to convert them into a set of dichotomous variables with the categories being one less than the total number of discrete categories. The variables were entered as a block in the regression analysis.

Table 3.21 presents the results of the regression analysis. The overall regression F-test was used to evaluate the model fit, and the null hypothesis that there is no linear relationship between the dependent and the independent variables was rejected ($F(15,6941) = 14.97$; $p < 0.001$). However, only 3.1 percent of the observed variability in the mean MPR was explained by the independent variables (R-square = 0.031). Based on the results of the analysis, being male, non-Hispanic white and the absence of CHD,

hypertension and diabetes was associated with an increase in MPR. The study hypotheses 2 to 9 are addressed following Table 3.21.

Table 3.21 Multiple Regression Analysis for "Medication Possession Ratio" and Demographic and Disease Condition Variables

Variables	Unstandardized Coefficients	Standardized Coefficients	t	Sig
	B	Beta		
Age at index date	.000	.014	1.129	.259
Gender (Male)[a]	.040	.068	5.510	.000*
Ethnicity (Black, non-Hispanic)[b]	-.086	-.127	-9.668	.000*
Ethnicity (Hispanic)[b]	-.078	-.130	-9.907	.000*
Ethnicity (American Indian or Alaskan Native)[b]	-.009	-.002	-.171	.864
Ethnicity (Asian or Pacific Islander)[b]	-.029	-.014	-1.139	.255
Diabetes prior to index date[c]	-.009	-.016	-1.203	.229
Diabetes developed during follow-up[c]	-.023	-.025	-1.992	.046*
Hypertension prior to index date[d]	-.019	-.034	-2.082	.037*
Hypertension developed during follow-up[d]	-.029	-.042	-2.802	.005*
CHD prior to index date[e]	-.024	-.037	-2.810	.005*
CHD developed during follow-up[e]	-.022	-.028	-2.202	.028*
Atherosclerosis prior to index date[f]	.009	.011	.915	.360
Atherosclerosis developed during follow-up[f]	.000	.000	-.035	.972
Total number of other prescriptions	.000	.003	.271	.786

$F(15,6941) = 14.97$; $p<0.001$, R-square = 0.031

N = 6,957

***p<0.05**

[a]Reference category is female.

[b]Reference category is white, non-Hispanic.

[c]Reference category is absence of diabetes.

[d]Reference category is absence of hypertension.

[e]Reference category is absence of CHD.

[f]Reference category is absence of atherosclerosis.

Hypothesis 2: The MPR will be higher for males than for females, controlling for age, ethnicity, presence of CHD, diabetes, hypertension, atherosclerotic diseases, and total number of prescriptions.

Based on the results of the multiple regression analysis presented in Table 3.21, a positive significant relationship was observed between the MPR and gender (Beta = 0.07, $p < 0.001$), controlling for age, ethnicity, and disease conditions. This implies that males had a higher MPR than females. Hence, hypothesis 2 was not rejected.

Hypothesis 3: The MPR will be higher for older patients than for younger patients, controlling for gender, ethnicity, presence of CHD, diabetes, hypertension, atherosclerotic disease, and total number of prescriptions.

Based on the results of the multiple regression analysis as presented in Table 3.21, there was no association between age and MPR (Beta = 0.014, $p = 0.259$), controlling for gender, ethnicity, disease conditions, and total number of prescriptions. Thus, hypothesis 3 was rejected as age was not related to MPR while controlling for other variables in the model.

Hypothesis 4: The MPR will be higher for non-Hispanic whites than for other ethnic groups, controlling for age, gender, presence of CHD, diabetes, hypertension, atherosclerotic diseases, and total number of prescriptions.

Based on the results of the multiple regression analysis as presented in Table 3.21, a negative relationship was observed between the mean MPR and ethnicity, with non-Hispanic blacks (Beta = -0.127, $p < 0.001$) and Hispanics (Beta = -0.130, $p < 0.001$) having a lower MPR as compared to non-Hispanic whites, controlling for age, gender,

disease conditions, and total number of prescriptions. Thus, hypothesis 4 was not rejected.

Hypothesis 5: *The MPR will be higher for secondary prevention CHD patients than for primary prevention CHD patients, controlling for age, gender, ethnicity, presence of diabetes, hypertension, atherosclerotic diseases, and total number of prescriptions.*

Based on the results of the multiple regression analysis as presented in Table 3.21, the MPR was lower for those having CHD a year prior to index date (Beta = -0.037, $p = 0.005$) and those who developed CHD during the follow-up period (Beta = -0.028, $p < 0.028$) as compared to those who did not have CHD, controlling for demographics and other disease conditions, and total number of prescriptions. With every one unit increase in the diagnosis for CHD at or prior to index date and during the follow-up period, MPR decreased by 0.024 and 0.022, respectively. Thus, hypothesis 5 was rejected as having a diagnosis for CHD before or after the index date was not positively related to MPR.

Hypothesis 6: *The MPR will be higher for diabetics than for non-diabetics, controlling for age, gender, ethnicity, presence of CHD, hypertension, atherosclerotic diseases, and total number of prescriptions.*

Based on the results of the multiple regression analysis as presented in Table 3.21, the MPR was lower for those patients who developed diabetes during the follow-up period (Beta = -0.025, $p = 0.046$) as compared to those who did not have diabetes, controlling for demographics, other disease conditions and total number of prescriptions. With every one unit increase in the number of diabetics prior to or at index date and during follow-up, the MPR decreased by 0.009 and 0.023 units, respectively. Thus,

hypothesis 6 was rejected as having a diagnosis for diabetes before or after the index date was not positively related to MPR.

Hypothesis 7: *The MPR will be higher for hypertensives than for non-hypertensives, controlling for age, gender, ethnicity, presence of CHD, diabetes, atherosclerotic diseases, and total number of prescriptions.*

Based on the results of the multiple regression analysis as presented in Table 3.21, patients who had hypertension a year prior to the index date (Beta = -0.034, p = 0.037) and those who developed hypertension during the follow-up period (Beta = -0.042, p = 0.005) had a lower MPR as compared to those who did not have hypertension, controlling for demographics, disease conditions, and total number of prescriptions. With every one unit increase in the diagnosis for hypertension prior to or at index date and during the follow-up period, MPR decreased by 0.019 and 0.029, respectively. Thus, hypothesis 7 was rejected.

Hypothesis 8: *The MPR will be higher for those patients with atherosclerotic diseases than for those without atherosclerotic diseases, controlling for age, gender, ethnicity, presence of CHD, diabetes, hypertension, and total number of prescriptions.*

Based on the results of the multiple regression analysis as presented in Table 3.21, no significant association was observed between MPR and the presence of atherosclerotic diseases at or prior to index date (Beta = 0.011, p = 0.360) or during the follow-up period (Beta = 0.000, p = 0.972), controlling for demographics, disease conditions, and total number of prescriptions. Thus, hypothesis 8 was rejected as having a diagnosis for

atherosclerotic diseases before or after the index date was neither significantly nor positively related to MPR.

Hypothesis 9: The MPR will be higher for those patients on a lower number of total prescriptions other than statins than for those on a higher number of prescriptions, controlling for age, gender, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic disease.

Based on the results of the multiple regression analysis as presented in Table 3.21, no significant association was observed between MPR and the total number of prescriptions other than statins (Beta = 0.003, p = 0.786), controlling for demographics and disease conditions. Thus, hypothesis 9 was rejected.

Objective 12: To determine if factors such as demographic characteristics (age, gender and ethnicity), type of CHD prevention, presence of diabetes, hypertension, and atherosclerotic diseases, and total number of other prescriptions are predictors of persistence to statin therapy.

Study objective 12, which is represented by hypotheses 10 through 17, was assessed using Cox regression analysis. Days until patients discontinue their statin therapy was the dependent variable in the model. Sixty days was used as a marker for discontinuation. The predictor variables in the model included patient's age at index date, gender, ethnicity, presence of CHD, diabetes, hypertension, atherosclerotic disease and the total number of prescriptions that the patient took during the two-year follow-up other than statins.

The Cox regression equation to test the study objectives is as follows:

$$\log hi(t) = \alpha(t) + \beta_1 xi_1 + \beta_2 xi_2 + \ldots\ldots + \beta_8 xi_8$$

where

hi = time to statin therapy discontinuation

$\alpha(t) = \log h_0(t)$, baseline hazard function

x_1 = age

x_2 = gender

x_3 = ethnicity

x_4 = presence of diabetes

x_5 = presence of CHD

x_6 = presence of hypertension

x_7 = presence of atherosclerotic disease

x_8 = total number of prescriptions other than statins

β = Regression coefficients for the change in the hazard ratio associated with a one unit change in the predictor variables

Table 3.22 shows the regression coefficients, Wald statistics, degrees of freedom, p values and the hazard ratio for each predictor variable, following which the study hypotheses pertaining to this study objective are tested. The test of model coefficients revealed that the variables reliably predicted the time to statin discontinuation since the null hypothesis of the likelihood of a chance model was rejected (Chi-square =190.36,

df =15 ; $p < 0.001$). In general, being male and white was associated with a lower hazard of becoming non-persistent whereas presence of disease conditions such as CHD, diabetes and hypertension was associated with a higher hazard of becoming non-persistent, controlling for other variables in the model.

Table 3.22: Cox Regression Analysis for "Time To Statin Therapy Discontinuation[#]" with Demographic and Disease Condition Variables

Variables	B	SE	Wald	df	Sig	Hazard Ratio	95.0% Confidence Interval for Hazard Ratio	
							Lower	Upper
Age at index date	-.002	.002	1.589	1	.207	.998	.994	1.001
Gender (Male)[a]	-.146	.036	16.190	1	.000*	.864	.805	.928
Ethnicity (Black, non-Hispanic)[b]	.369	.043	72.337	1	.000*	1.446	1.328	1.575
Ethnicity (Hispanic)[b]	.315	.040	63.690	1	.000*	1.371	1.269	1.481
Ethnicity (American Indian or Alaskan)[b]	.610	.237	6.592	1	.010*	1.840	1.155	2.930
Ethnicity (Asian or Pacific Islander)[b]	.339	.124	7.502	1	.006*	1.403	1.101	1.788
Diabetes prior to index date[c]	.109	.038	8.109	1	.004*	1.115	1.035	1.203
Diabetes developed during follow-up[c]	.109	.056	3.762	1	.052	1.115	.999	1.244
Hypertension prior to index date[d]	.094	.047	4.045	1	.044*	1.099	1.002	1.205
Hypertension developed during follow-up[d]	.105	.053	3.978	1	.046*	1.111	1.002	1.233
CHD prior to index date[e]	.123	.042	8.504	1	.004*	1.131	1.041	1.229
CHD developed during follow-up[e]	.127	.048	7.012	1	.008*	1.136	1.034	1.248
Atherosclerosis prior to index date[f]	-.105	.051	4.219	1	.040*	.900	.814	.995
Atherosclerosis developed during follow-up[f]	.010	.048	.044	1	.833	1.010	.919	1.111
Total number of prescriptions	.001	.002	.285	1	.594	1.001	.997	1.005

-2 Log Likelihood = 62364.7 Overall Chi-square = 190.36, df = 15, ($p<0.001$); N = 6,957

***p <0.05**

[#]60 days without receiving a statin refill was used as a marker for discontinuation.

[a]Reference category is female.

[b]Reference category is white, non-Hispanic.

[c]Reference category is absence of diabetes.

[d]Reference category is absence of hypertension.

[e]Reference category is absence of CHD.

[f]Reference category is absence of atherosclerosis.

Hypothesis 10: Females will have a higher hazard of becoming non-persistent to statin therapy than males controlling for age, ethnicity, presence of CHD, hypertension, diabetes, atherosclerotic diseases, and total number of prescriptions.

Based on the results of the Cox regression analysis presented in Table 3.22, males had a 13 percent lower hazard of becoming non-persistent as compared to females (Hazard Ratio = 0.864; 95% CI: 0.805-0.928; $p < 0.001$), controlling for age, ethnicity, disease conditions, and total number of prescriptions. Thus, hypothesis 10 was not rejected.

Hypothesis 11: Younger patients will have a higher hazard of becoming non-persistent to statin therapy than older patients, controlling for gender, ethnicity, presence of CHD, hypertension, diabetes, atherosclerotic diseases, and total number of prescriptions.

Based on the results of the Cox regression analysis presented in Table 3.22, the hazard of becoming non-persistent did not differ with age, controlling for gender, ethnicity, disease conditions, and total number of prescriptions (Hazard Ratio = 0.998 95% CI: 0.994-1.001; $p = 0.207$). Thus, hypothesis 11 was rejected.

Hypothesis 12: Other ethnic minorities will have a higher hazard of becoming non-persistent to statin therapy than non-Hispanic whites, controlling for age, gender, presence of CHD, hypertension, diabetes, atherosclerotic diseases, and total number of prescriptions.

Based on the results of the Cox regression analysis presented in Table 3.22, the hazard of becoming non-persistent with statin therapy was higher in non-Hispanic blacks compared to non-Hispanic whites, (Hazard Ratio = 1.446; 95% CI: 1.328-1.575; $p < 0.001$), Hispanics (Hazard Ratio = 1.371; 95% CI: 1.269-1.481, $p < 0.001$), American

Indians or Alaskans (Hazard Ratio = 1.840; 95% CI: 1.155-2.930; p = 0.010), and Asians or Pacific Islanders (Hazard Ratio = 1.403; 95% CI: 1.101-1.788; p = 0.006), controlling for age, gender, disease conditions, and total number of prescriptions. Thus, hypothesis 12 was not rejected.

Hypothesis 13: Patients without CHD will have a higher hazard of becoming non-persistent to statin therapy than those with CHD, controlling for age, gender, ethnicity, presence of hypertension, diabetes, atherosclerotic diseases, and total number of prescriptions.

Based on the results of the Cox regression analysis presented in Table 3.22, contrary to the hypothesis, patients with CHD in the year prior to the index date (Hazard Ratio = 1.131; 95% CI: 1.041-1.229; p = 0.004) and those who developed CHD in the follow-up period (Hazard Ratio = 1.136; 95% CI: 1.034-1.248; p = 0.008) had a greater hazard of becoming non-persistent than those who did not have a diagnosis for CHD, controlling for demographic characteristics, other disease conditions, and total number of prescriptions. Thus, hypothesis 13 was rejected.

Hypothesis 14: Patients without diabetes will have a higher hazard of becoming non-persistent to statin therapy than those with diabetes, controlling for age, gender, ethnicity, presence of CHD, hypertension, atherosclerotic diseases, and total number of prescriptions.

Based on the results of the Cox regression analysis presented in Table 3.22, contrary to the hypothesis, patients with a diagnosis for diabetes in the year prior to the index date were at a greater hazard (Hazard Ratio = 1.115; 95% CI: 1.035-1.203; p = 0.004) of becoming non-persistent than those who did not have diabetes, controlling

for demographic characteristics, other disease conditions, and total number of prescriptions. The hazard of becoming non-persistent to statin therapy did not differ significantly between those patients who did not have diabetes versus those who developed diabetes during the follow-up period (Hazard Ratio = 1.115; 95% CI: 0.999-1.244; p = 0.052). Thus, hypothesis 14 was rejected based on having diabetes prior to index date.

Hypothesis 15: *Patients without hypertension will have a higher hazard of becoming non-persistent to statin therapy than those with hypertension, controlling for age, gender, ethnicity, presence of CHD, diabetes, atherosclerotic diseases, and total number of prescriptions.*

Based on the results of the Cox regression results presented in Table 3.22, patients with a diagnosis for hypertension in the year prior to index date (Hazard Ratio = 1.099; 95% CI: 1.002-1.205; p = 0.044) or in the follow-up period (Hazard Ratio = 1.111; 95% CI: 1.002-1.233; p = 0.046) had a greater hazard of becoming non-persistent than those who did not have a diagnosis for hypertension, controlling for demographic characteristics, other disease conditions, and total number of prescriptions. Thus, hypothesis 15 was rejected.

Hypothesis 16: *Patients without atherosclerotic diseases will have a higher hazard of becoming non-persistent to statin therapy than those with atherosclerotic diseases controlling for age, gender, ethnicity, presence of CHD, diabetes, hypertension, and total number of prescriptions.*

Based on the results of the Cox regression results presented in Table 3.22, patients with a diagnosis for atherosclerosis in the year prior had a slightly lower hazard (Hazard Ratio = 0.900; 95% CI: 0.814-0.995; p = 0.04) of becoming non-persistent than those who did not have atherosclerosis. However, the hazard of becoming non-persistent did not differ significantly between those who did not have atherosclerosis and those who developed atherosclerosis during the follow-up period (Hazard Ratio = 1.010; 95% CI: 0.919-1.111; p = 0.833). Thus, hypothesis 16 was not rejected based on presence of atherosclerotic disease prior to index date.

Hypothesis 17: *Patients on a greater number of total prescriptions other than statins will have a higher hazard of becoming non-persistent than those on fewer prescriptions, controlling for age, gender, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases.*

Based on the results of the Cox regression analysis presented in Table 3.22, the number of prescriptions that the patient was on during the study period did not have any effect on the hazard rate of becoming non-persistent (Hazard Ratio = 1.001; 95% CI: 0.997 – 1.005; p = 0.594), controlling for demographic characteristics and disease conditions. Thus, hypothesis 17 was rejected.

Evaluation of How Well Physicians Follow Lipid and Safety Monitoring Guidelines

The study goal aimed at evaluating how well physicians follow lipid and safety monitoring guidelines (objectives 13 through 22) were assessed using hypotheses 18 through 76. The outcome variables (lipid and liver function tests) were dichotomized with 1 = presence of a test and 0 = absence of a test. Seven logistic regression models were used. The coding schemes for the predictor variables in the model are listed in Table 3.23. The model fit was assessed using the model chi-square test and the Hosmer and Lemeshow statistic.[437]

The model chi-square test presents the improvement in the model fit due to the predictor variables compared to a constant only model. A model chi-square significant at a 0.05 level or less, leads to the rejection of the null hypothesis that there is no difference between the constant only model and the model with the predictor variables. In other words, an acceptable model fit will produce a significant model chi-square.

The Hosmer and Lemeshow goodness-of-fit test groups cases based on the predicted probabilities and computes a chi-square from the observed and expected frequencies. If the statistic is significant at 0.05 level or less, the null hypothesis that there is no difference between the observed and the predicted values of the predictor variables is rejected. In other words, an acceptable model will produce a non-significant chi-square for the Hosmer and Lemeshow goodness-of-fit test.

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[437] Hosmer DW, Lemeshow S. Assessing the fit of the model. *Applied Logistic Regression*. New York: John Wiley & Sons; 1989:135-173.

Table 3.23: Coding of Variables to be Included in Logistic Regression Models

Variables	Variable Codes
Age	Age at the index date – continuous variable
Gender	1=Male; 2=Female*
Ethnicity	1=Non-Hispanic whites*; 2=Non-Hispanic blacks; 3=Hispanics; 4=American Indian or Alaskan; 5=Asian or Pacific Islander
Presence of CHD	1=Yes; 2=No*
Presence of diabetes	1=Yes; 2=No*
Presence of hypertension	1=Yes; 2=No*
Presence of atherosclerotic disease	1=Yes; 2=No*
Physician specialty at index date	1=Cardiologists*; 2=Family practice/general practice; 3=Internal medicine; 4=Other
Prior lipid test	1=Yes; 2=No*
Prior LFT	1=Yes; 2=No*

*Reference category in the model.

Objective 16: To assess the predictors of the occurrence of lipid monitoring tests at baseline (within three months prior to start of therapy).

Lipid monitoring was assessed three months prior to start of therapy. Hypotheses 18 to 24 addressing this study objective were tested using logistic regression analysis, with age, gender, ethnicity, presence of a diagnosis for CHD, diabetes, hypertension, and atherosclerotic disease as the predictor variables in the model.

The following logistic regression model was used to test the hypotheses:

$\ln(OR) = \alpha + \beta_1$ age $+ \beta_2$ gender $+ \beta_3$ ethnicity $+ \beta_4$ CHD $+ \beta_5$ diabetes $+ \beta_6$ hypertension $+ \beta_7$ atherosclerotic disease $+ \varepsilon$

where:

ln(OR) = overall logit of the likelihood of a lipid test at baseline.

β_i (i=1,2,3,4,5,6,7)= coefficient for the change in ln(OR) associated with a one unit change in age, gender, ethnicity, type of CHD prevention, presence of diabetes as a risk factor, presence of hypertension as a risk factor, and presence of atherosclerotic disease.

α = intercept

ε = error term

Female gender, older age, being non-Hispanic Black, as well as presence of disease conditions such as CHD was associated with a decreased likelihood of lipid testing. However, being Hispanic and presence of disease conditions such as diabetes and hypertension was associated with an increased likelihood of lipid testing. The results of the logistic regression analysis are presented below in Table 3.24, following which hypotheses 18 to 24 are discussed. Based on the Hosmer-Lemeshow statistic ($p > 0.05$), as well as the overall model chi-square ($p < 0.001$), the model presented an acceptable fit.

Table 3.24: Logistic Regression Analysis to Assess Predictors of Lipid Monitoring within Three Months Prior to Start of Statin Therapy

Variables	B	S.E.	Wald	df	Sig	Odds Ratio	95.0% Confidence Interval for Odds Ratio	
							Lower	Upper
Age at index date	-.009	.003	10.130	1	.001*	.991	.986	.997
Gender (Male)	-.298	.053	32.266	1	.000*	.742	.669	.823
Ethnicity (Black, non-Hispanic)	-.405	.066	37.340	1	.000*	.667	.586	.759
Ethnicity (Hispanic)	.187	.058	10.562	1	.001*	1.206	1.077	1.350
Ethnicity (American Indian or Alaskan)	.005	.389	.000	1	.991	1.005	.468	2.154
Ethnicity (Asian or Pacific Islander)	.324	.188	2.968	1	.085	1.383	.956	1.999
Diabetes prior to index date	.155	.052	8.984	1	.003*	1.168	1.055	1.292
Hypertension prior to index date	.645	.054	142.524	1	.000*	1.907	1.715	2.120
CHD prior to index date	-.233	.060	14.950	1	.000*	.793	.704	.892
Atherosclerosis prior to index date	-.099	.074	1.800	1	.180	.906	.784	1.047

Hosmer and Lemeshow Goodness of fit test: Chi-square = 3.837; df = 8; p = 0.872; Model Chi-square = 300.708; df = 13; p < 0.001

***p < 0.05**

N = 7,054

[a]Reference category is female.

[b]Reference category is whites.

[c]Reference category is absence of diabetes.

[d]Reference category is absence of hypertension.

[e]Reference category is absence of CHD.

[f]Reference category is absence of atherosclerosis.

[g]Reference category is cardiologists.

Hypothesis 18: The likelihood of a lipid test at baseline will be higher for males than for females, controlling for age, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases.

Based on the results of the logistic regression analysis presented in Table 3.24, males (Odds Ratio (OR) = 0.742; 95% CI: 0.669-0.823; $p < 0.001$) were associated with a decreased odds of getting a lipid test as compared to females, controlling for age, ethnicity, and disease conditions . Thus, hypothesis 18 was rejected.

Hypothesis 19: The likelihood of a lipid test at baseline will be higher for older patients for than younger patients, controlling for gender, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases.

Based on the results of the logistic regression analysis presented in Table 3.24, older age (OR = 0.991; 95% CI: 0.986-0.997; $p = 0.001$) was associated with a slight decrease in the odds of getting a lipid test compared to younger patients, controlling for gender, ethnicity, and presence of disease conditions. Thus, hypothesis 19 was rejected.

Hypothesis 20: The likelihood of a lipid test at baseline will be higher for non-Hispanic whites than for other age, ethnic groups, controlling for gender, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases.

Based on the results of the logistic regression analysis presented in Table 3.24, being non-Hispanic black (OR = 0.667; 95% CI: 0.586-0.759; $p < 0.001$) was associated with decreased odds of getting a lipid test than non-Hispanic whites. However, Hispanics were 1.2 times more likely to get a lipid test compared to non-Hispanic whites ($p = 0.001$). Asian/Pacific Islanders (OR = 1.383; 95% CI: 0.956 – 1.999; $p = 0.085$) were associated with an increased odd of receiving a lipid test compared to non-

Hispanic whites, controlling for age, gender and disease conditions; however, the results were statistically non-significant. The odds of receiving a lipid test did not differ significantly between American Indian/Alaskan (OR = 1.005; 95% CI: 0.468 – 2.154; p = 0.991) and non-Hispanic whites, controlling for age, gender and disease conditions. Based on these results, hypothesis 20 was rejected.

Hypothesis 21: The likelihood of a lipid test at baseline will be higher for patients with CHD than for those without CHD, controlling for age, gender, ethnicity, presence of diabetes, hypertension, and atherosclerotic diseases.

Based on the results of the logistic regression analysis presented in Table 3.24, patients with CHD (OR = 0.793; 95% CI: 0.704-0.892; p < 0.001) had a decreased likelihood of getting a lipid test compared to those without CHD, controlling for demographic characteristics and other disease conditions. Thus, hypothesis 21 was rejected.

Hypothesis 22: The likelihood of a lipid test at baseline will be higher for patients with diabetes than for those without diabetes, controlling for age, gender, ethnicity, presence of CHD, hypertension, and atherosclerotic diseases.

Based on the results of the logistic regression analysis presented in Table 3.24, patients with diabetes (OR = 1.168; 95% CI: 1.055-1.292; p = 0.003) had a greater likelihood of having their lipid levels tested compared to those without diabetes, controlling for demographic characteristics and other disease conditions. Thus, hypothesis 23 was not rejected.

Hypothesis 23: The likelihood of a lipid test at baseline will be higher for patients with hypertension than for those without hypertension, controlling for age, gender, ethnicity, presence of CHD, diabetes, and atherosclerotic diseases.

Based on the results of the logistic regression analysis presented in Table 3.24, patients with hypertension (OR = 1.907; 95% CI: 1.715-2.210; $p < 0.001$) in the year prior to the index date had a higher likelihood of having their lipid levels tested compared to those without hypertension. Thus, hypothesis 23 was not rejected.

Hypothesis 24: The likelihood of a lipid test at baseline will be higher for patients with atherosclerotic diseases than for those without atherosclerotic diseases, controlling for age, gender, ethnicity, presence of CHD, diabetes, and hypertension.

Based on the results of the logistic regression analysis presented in Table 3.24, there was no significant differences in the likelihood of a lipid test between those patients with atherosclerotic diseases versus those without (OR = 0.906; 95% CI: 0.784-1.047; $p = 0.180$), controlling for demographic characteristics, and other disease conditions. Thus, hypothesis 24 was rejected.

Objective 17: To assess the predictors of the occurrence of lipid monitoring after the start of therapy (within three months, but not earlier than six weeks since* the start of *therapy).

Lipid monitoring was assessed within three months (but not earlier than six weeks) from the start of statin therapy. Hypotheses 25 to 32, addressing this study objective, were tested using logistic regression analysis with age, gender, ethnicity, presence of a diagnosis for CHD, diabetes, hypertension and atherosclerotic disease, physician specialty and lipid testing at baseline as the predictor variables in the model.

The following logistic regression model was used to test hypotheses 25 to 32.

$\ln(OR) = \alpha + \beta_1$ age $+ \beta_2$ gender $+ \beta_3$ ethnicity $+ \beta_4$ CHD $+ \beta_5$ diabetes $+ \beta_6$ hypertension $+ \beta_7$ atherosclerotic disease $+ \beta_8$ physician specialty at index date $+ \beta_9$ prior lipid test $+ \varepsilon$

where:

$\ln(OR)$ = overall logit of the likelihood of a lipid test at baseline.

β_i (i=1,2,3,4,5,6,7,8,9) = coefficient for the change in ln(OR) associated with a one unit change in gender, ethnicity, type of CHD prevention, presence of diabetes as a risk factor, presence of hypertension as a risk factor, presence of atherosclerotic disease, physician specialty, and presence of lipid test at baseline.

α = intercept

ε = error term

Being white, having CHD and a lipid test prior to index date were significant predictors of lipid testing after the start of therapy, controlling for age, gender, other disease conditions, and physician specialty at index date. The results of the logistic regression analysis are presented below in Table 3.25, following which hypotheses 25 to 33 are discussed. Based on the Hosmer-Lemeshow statistic ($p > 0.05$), as well as the overall model chi-square ($p < 0.001$), the model presented an acceptable fit.

Table 3.25: Logistic Regression Analysis to Assess Predictors of Lipid Monitoring Within Three Months Following Start of Statin Therapy

Variables	B	S.E.	Wald	df	Sig	Odds Ratio	95.0% Confidence Interval for Odds Ratio	
							Lower	Upper
Age at index date	-.006	.004	2.455	1	.117	.994	.986	1.002
Gender (Male)[a]	.142	.077	3.460	1	.063	1.153	.992	1.339
Ethnicity (Black, non-Hispanic)[b]	-.218	.106	4.226	1	.040*	.804	.653	.990
Ethnicity (Hispanic)[b]	.156	.082	3.625	1	.057	1.169	.995	1.373
Ethnicity (American Indian or Alaskan)[b]	.639	.501	1.630	1	.202	1.895	.710	5.056
Ethnicity (Asian or Pacific Islander)[b]	-.102	.286	.128	1	.721	.903	.516	1.580
Diabetes prior to index date[c]	.015	.076	.039	1	.844	1.015	.874	1.179
Hypertension prior to index date[d]	.131	.080	2.676	1	.102	1.140	.974	1.333
CHD prior to index date[e]	.266	.090	8.714	1	.003*	1.305	1.093	1.556
Atherosclerosis prior to index date[f]	.145	.104	1.963	1	.161	1.156	.944	1.416
Physician specialty (Family practice/general practice)[g]	-.047	.151	.097	1	.755	.954	.710	1.282
Physician specialty (Internal medicine)[g]	.011	.150	.005	1	.944	1.011	.753	1.357
Physician specialty (Others)[g]	-.093	.168	.307	1	.579	.911	.655	1.267
Lipid test three months prior to index date[h]	1.437	.079	334.613	1	.000*	4.207	3.607	4.908

Hosmer and Lemeshow Goodness of fit test: Chi-square = 8.244; df = 8; p = 0.410; Model Chi-square = 443.846; df = 14; p < 0.001 ***p < 0.05**

N = 6,203; [a]Reference category is female.

[b]Reference category is whites.

[c]Reference category is absence of diabetes.

[d]Reference category is absence of hypertension.

[e]Reference category is absence of CHD.

[f]Reference category is absence of atherosclerosis.

[g]Reference category is cardiologists.

[h]Reference category is absence of lipid test

Hypothesis 25: The likelihood of a lipid test after start of therapy will be higher for males than for females controlling for age, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.

Based on the results of the logistic regression analysis presented in Table 3.25, the likelihood of a lipid test after start of therapy did not differ with respect to gender (OR = 1.153; 95% CI: 0.992-1.339; p = 0.063) controlling for age, ethnicity, disease conditions, physician specialty, and prior lipid testing. Thus, hypothesis 25 was rejected.

Hypothesis 26: The likelihood of a lipid test after start of therapy will be higher for older patients than for younger patients, controlling for gender, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.

Based on the results of the logistic regression analysis presented in Table 3.25, the likelihood of a lipid test at start of therapy did not differ with age (OR = 0.994, 95% CI: 0.986-1.002, p = 0.117), controlling for gender, ethnicity, disease conditions, physician specialty, and prior lipid testing. Thus, hypothesis 26 was rejected.

Hypothesis 27: The likelihood of a lipid test after start of therapy will be higher for non-Hispanic whites than for other ethnic groups, controlling for age, gender, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.

Based on the results of the logistic regression analysis presented in Table 3.25, non-Hispanic blacks had a decreased likelihood of getting lipid tests compared to non-Hispanic whites (OR = 0.804, 95% CI: 0.653-0.990; p = 0.04). The likelihood of a lipid test did not differ significantly between non-Hispanic whites and Hispanics (OR = 1.169; 95% CI: 0.995-1.373; p = 0.057). American Indian or Alaskan were 1.8 times more

likely to get a lipid test compared to non-Hispanic whites (OR = 1.895; 95% CI: 0.710-5.056); however, the result was not statistically significant (p = 0.202). Based on the results, hypothesis 27 was rejected.

Hypothesis 28: The likelihood of a lipid test after start of therapy will be higher for patients with CHD than for those without CHD, controlling for age, gender, ethnicity, presence of diabetes, hypertension, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.

Based on the results of the logistic regression analysis presented in Table 3.25, patients with a diagnosis of CHD at or a year prior to the index date were more likely to get a lipid test than those without a diagnosis for CHD (OR = 1.305; 95% CI: 1.093-1.556; p = 0.003), controlling for demographic characteristics, other disease conditions, physician specialty, and lipid testing prior to index date. Thus, hypothesis 28 was not rejected.

Hypothesis 29: The likelihood of a lipid test after start of therapy will be higher for patients with diabetes than for those without diabetes, controlling for age, gender, ethnicity, presence of CHD, hypertension, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.

Based on the results of the logistic regression analysis presented in Table 3.25, patients with a diagnosis of diabetes did not differ significantly with respect to lipid monitoring as compared to those without a diagnosis for diabetes (OR = 1.015; 95% CI: 0.874-1.179; p = 0.844), controlling for demographic characteristics, other disease conditions, physician specialty, and lipid testing prior to index date. Thus, hypothesis 29 was rejected.

Hypothesis 30: The likelihood of a lipid test after start of therapy will be higher for patients with hypertension than for those without hypertension, controlling for age, gender, ethnicity, presence of CHD, diabetes, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.

Based on the results of the logistic regression analysis presented in Table 3.25, patients with a diagnosis of hypertension did not differ significantly with respect to lipid monitoring as compared to those without a diagnosis for hypertension, (OR = 1.140; 95% CI: 0.974-1.333; p = 0.102) controlling for demographic characteristics, other disease conditions, physician specialty, and lipid testing prior to index date. Thus, hypothesis 30 was rejected.

Hypothesis 31: The likelihood of a lipid test after start of therapy will be higher for patients with atherosclerotic diseases than for those without atherosclerotic diseases, controlling for age, gender, ethnicity, presence of CHD, diabetes, and hypertension, physician specialty, and lipid testing prior to index date.

Based on the results of the logistic regression analysis presented in Table 3.25, patients with a diagnosis patients of atherosclerotic diseases did not differ significantly with respect to lipid monitoring as compared to those without a diagnosis for atherosclerotic diseases (OR = 1.156; 95% CI: 0.944-1.416; p = 0.161), controlling for demographic characteristics, other disease conditions, physician specialty, and lipid testing prior to index date. Thus, hypothesis 31 was rejected.

Hypothesis 32: The likelihood of a lipid test after start of therapy will be higher for patients treated by a cardiologist at index date than for those treated by other physician specialty, controlling for age, gender, ethnicity, presence of CHD, diabetes, hypertension and atherosclerotic diseases, and lipid testing prior to index date.

Based on the results of the logistic regression analysis presented in Table 3.25, the likelihood of a lipid test at the start of therapy did not differ significantly for those patients treated by a cardiologist at index date compared to family practice/general practice (OR = 0.954; 95% CI: 0.710-1.282; p = 0.755), internal medicine (OR = 1.011; 95% CI: 0.753-1.357; p = 0.944) or other physician specialty (OR = 0.911; 95% CI: 0.655-1.267; p = 0.579). Thus, hypothesis 32 was rejected.

Hypothesis 33: The likelihood of a lipid test after start of therapy will be higher for patients with lipid tests at baseline than those without lipid tests at baseline, controlling for age, gender, ethnicity, presence of CHD, diabetes, and hypertension, atherosclerotic diseases, and physician specialty.

Based on the results of the logistic regression analysis presented in Table 3.25, the the presence of a lipid test prior to the index date was a significant predictor for lipid test after the start of therapy. Patients who had a lipid test prior to the start of therapy were 4.2 times more likely to get a lipid test after the start of therapy (OR = 4.207; 95% CI: 3.607-4.908; p < 0.001). Thus, hypothesis 33 was not rejected.

Objective 18: To assess the predictors of the occurrence of lipid monitoring (within three months, but not earlier than six weeks) from the initial change in statin type.

Lipid monitoring was assessed within three months (but not earlier than six weeks) from the initial change in statin type. Hypotheses 34 to 42, addressing this study objective, were tested using logistic regression with age, gender, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic disease, physician specialty at index date and lipid testing prior to start of therapy as the predictor variables.

The following logistic regression model was used to address the hypotheses:

$\ln(OR) = \alpha + \beta_1$ age $+ \beta_2$ gender $+ \beta_3$ ethnicity $+ \beta_4$ CHD $+ \beta_5$ diabetes $+ \beta_6$ hypertension $+ \beta_7$ atherosclerotic disease $+ \beta_8$ physician specialty at index date $+ \beta_9$ prior lipid test $+ \varepsilon$

where:

ln(OR) = overall logit of the likelihood of a lipid test at baseline.

β_i (i=1,2,3,4,5,6,7,8,9)= coefficient for the change in ln(OR) associated with a one unit change in gender, ethnicity, type of CHD prevention, presence of diabetes as a risk factor, presence of hypertension as a risk factor, presence of atherosclerotic disease, physician specialty, and presence of lipid test at baseline.

α = intercept

ε = error term

The only significant predictor of lipid monitoring after the initial change in statin type was baseline lipid monitoring, controlling for other variables. The results of the logistic regression analysis are presented in Table 3.26 below, following which

hypotheses 34 to 42 are discussed. Based on the Hosmer-Lemeshow statistic ($p > 0.05$), as well as the overall model chi-square ($p < 0.001$), the model presented an acceptable fit.

Table 3.26: Logistic Regression Analysis to Assess Predictors of Lipid Monitoring Within Three Months of a Change in Statin Type

Variables	B	S.E.	Wald	df	Sig	Odds Ratio	95.0% Confidence Interval for Odds Ratio	
							Lower	Upper
Age at index date	-.006	.011	.339	1	.560	.994	.973	1.015
Gender (Male)[a]	.118	.193	.377	1	.539	1.125	.772	1.641
Ethnicity (Black, non-Hispanic)[b]	-.294	.273	1.167	1	.280	.745	.437	1.271
Ethnicity (Hispanic)[b]	.187	.205	.837	1	.360	1.206	.807	1.802
Ethnicity (American Indian or Alaskan/Asian or Pacific Islander)[b]	.761	.448	2.886	1	.089	2.141	.890	5.151
Diabetes prior to index date[c]	.082	.188	.189	1	.664	1.085	.751	1.569
Hypertension prior to index date[d]	-.004	.199	.000	1	.985	.996	.674	1.473
CHD prior to index date[e]	.172	.230	.556	1	.456	1.187	.756	1.864
Atherosclerosis prior to index date[f]	.050	.277	.033	1	.857	1.051	.611	1.811
Physician specialty (Family practice/general practice)[g]	.696	.516	1.820	1	.177	2.005	.730	5.511
Physician specialty (Internal medicine)[g]	.690	.515	1.795	1	.180	1.993	.727	5.467
Physician specialty (Others)[g]	.620	.552	1.264	1	.261	1.860	.631	5.483
Lipid test three months prior to index date[h]	.889	.189	22.065	1	.000*	2.432	1.679	3.525

Hosmer and Lemeshow Goodness of fit test: Chi-square = 11.270; df = 8; p = 0.187; Model Chi-square = 37.238; df = 13; p < 0.001; ***p < 0.05**
N = 1,062; [a]Reference category is female.
[b]Reference category is whites, non-Hispanic.
[c]Reference category is absence of diabetes.
[d]Reference category is absence of hypertension.
[e]Reference category is absence of CHD.
[f]Reference category is absence of atherosclerosis.
[g]Reference category is cardiologists.
[h]Reference category is absence of lipid test.

Hypothesis 34: The likelihood of a lipid test after an initial change in statin type will be higher for males than for females controlling for age, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.

Based on the results of the logistic regression analysis presented in Table 3.26, lipid testing after the initial change in statin type did not differ by gender (OR = 1.125; 95% CI: 0.772-1.641; p = 0.539) controlling for age, ethnicity, disease conditions, physician specialty, and lipid monitoring at baseline. Thus, hypothesis 34 was rejected.

Hypothesis 35: The likelihood of a lipid test after an initial change in statin type will be higher for older patients than for younger patients, controlling for age, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.

Based on the results of the logistic regression analysis presented in Table 3.26, the likelihood of receiving a lipid test after an initial change in statin type did not differ significantly with age (OR = 0.994; 95% CI: 0.973-1.015; p = 0.560), controlling for gender, ethnicity, disease conditions, physician specialty, and lipid monitoring at baseline. Thus, hypothesis 35 was rejected.

Hypothesis 36: The likelihood of a lipid test after an initial change in statin type will be higher for non-Hispanic whites than for other ethnic groups, controlling for age, gender, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.

Based on the results of the logistic regression analysis presented in Table 3.26, there was no significant difference in the likelihood of receiving a lipid test after the initial change in statin type between non-Hispanic whites and non-Hispanic blacks (OR =

0.745; 95% CI: 0.437-1.271; p = 0.280). Hispanics were 1.2 times more likely to receive the test compared to non-Hispanic whites (OR = 1.206; 95% CI: 0.807-1.802; p = 0.360), however, this result was not statistically significant (p = 0.360). Similarly, American Indian/Alaskan or Asian or Pacific Islanders were twice as likely than non-Hispanic whites to receive the lipid tests, however the confidence interval for the odds ratio was large (OR = 2.141; 95% CI: 0.809-5.151; p = 0.089) and the result was not statistically significant. Thus, hypothesis 36 was rejected.

Hypothesis 37: The likelihood of a lipid test after an initial change in statin type will be higher for patients with CHD than for those without CHD, controlling for age, gender, ethnicity, presence of diabetes, hypertension, and atherosclerotic diseases, physician specialty and lipid testing prior to index date.

Based on the results of the logistic regression analysis presented in Table 3.26, the likelihood of lipid test following an initial change in statin type did not differ significantly between those with and without CHD (OR = 1.187; 95% CI: 0.756-1.864; p = 0.456), controlling for demographic characteristics, other disease conditions, physician specialty, and lipid testing prior to index date. Thus, hypothesis 37 was rejected.

Hypothesis 38: The likelihood of a lipid test after an initial change in statin type will be higher for patients with diabetes than for those without diabetes, controlling for age, gender, ethnicity, presence of CHD, hypertension, and atherosclerotic diseases, physician specialty and lipid testing prior to index date.

Based on the results of the logistic regression analysis presented in Table 3.26, the likelihood of a lipid test after an initial change in statin type did not differ significantly between diabetics versus non-diabetics (OR = 1.085; 95% CI: 0.751-1.569; p = 0.664),

controlling for demographic characteristics, other disease conditions, physician specialty and lipid testing prior to index date. Thus, hypothesis 38 was rejected.

Hypothesis 39: The likelihood of a lipid test after an initial change in statin type will be higher for patients with hypertension than for those without hypertension, controlling for age, gender, ethnicity, presence of CHD, diabetes, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.

Based on the results of the logistic regression analysis presented in Table 3.26, the likelihood of a lipid test after an initial change in statin type did not differ significantly between hypertensives versus non-hypertensives (OR = 0.996; 95% CI: 0.674-1.473; p = 0.985), controlling for demographic characteristics, other disease conditions, physician specialty, and lipid testing prior to index date. Thus, hypothesis 39 was rejected.

Hypothesis 40: The likelihood of a lipid test after an initial change in statin type will be higher for patients with atherosclerotic diseases than for those without atherosclerotic diseases, controlling for age, gender, ethnicity, presence of CHD, diabetes, and hypertension, physician specialty, and lipid testing prior to index date.

Based on the results of the logistic regression analysis presented in Table 3.26, the likelihood of a lipid test after an initial change in statin type did not differ significantly between those with atherosclerotic disease versus those without (OR = 1.051; 95% CI: 0.611-1.811; p = 0.857), controlling for demographic characteristics, other disease conditions, physician specialty and lipid testing prior to index date. Thus, hypothesis 40 was rejected.

Hypothesis 41: The likelihood of a lipid test after an initial change in statin type will be higher for patients treated by a cardiologist at index than for those treated by other physician specialty, controlling for age, gender, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, and lipid testing prior to index date.

Based on the results of the logistic regression analysis presented in Table 3.26, patients treated by a family practice/general practice physician at index date were twice as likely to receive lipid tests after an initial change in statin dose as compared to cardiologists. However, the result was statistically non-significant ($p = 0.177$), and the confidence interval for the odds ratio was large (95% CI: 0.730-5.511). Similar results were obtained for physician with specializations in internal medicine (OR = 1.993; 95% CI: 0.727-5.467; $p = 0.180$) and other specialties (OR = 1.860; 95% CI: 0.631-5.483; $p = 0.261$). Thus, hypothesis 41 was rejected.

Hypothesis 42: The likelihood of a lipid test after start of therapy will be higher for patients with lipid tests at baseline than those without lipid tests at baseline, controlling for age, gender, ethnicity, presence of CHD, diabetes, and hypertension, atherosclerotic diseases, and physician specialty.

Based on the results of the logistic regression analysis presented in Table 3.26, the presence of a lipid test prior to the index date was a significant predictor for lipid monitoring after the initial change in statin type. Patients who had a lipid test prior to the start of therapy were 2.4 times more likely to get a lipid test after the change in statin type (OR = 2.432; 95% CI: 1.679-3.524; $p < 0.001$). Thus, hypothesis 42 was not rejected.

Objective 19: To assess the predictors of the occurrence of lipid monitoring (within three months, but not earlier than six weeks) following the initial change in statin dose.

Lipid monitoring was assessed within three months (but not earlier than six weeks) following an initial change in statin dose. Hypotheses 43 to 51 that addressed this study objective were tested using logistic regression with age, gender, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic disease, physician specialty at index date, and lipid monitoring at baseline as the predictor variables.

The following logistic regression model was used to assess predictors of lipid monitoring after initial change in statin dose:

$\ln(OR) = \alpha + \beta_1$ age $+ \beta_2$ gender $+ \beta_3$ ethnicity $+ \beta_4$ CHD $+ \beta_5$ diabetes $+ \beta_6$ hypertension $+ \beta_7$ atherosclerotic disease $+ \beta_8$ physician specialty at index date $+ \beta_9$ prior lipid test $+ \varepsilon$

where:

ln(OR) = overall logit of the likelihood of a lipid test after initial change in statin dose.

β_i (i=1,2,3,4,5,6,7,8,9) = coefficient for the change in ln(OR) associated with a one unit change in gender, ethnicity, type of CHD prevention, presence of diabetes as a risk factor, presence of hypertension as a risk factor, presence of atherosclerotic disease, physician specialty, and presence of lipid test at baseline.

α = intercept

ε = error term

The only significant predictor of lipid monitoring after the initial change in statin dose was baseline lipid monitoring, controlling for other variables. The results of the logistic regression analysis are presented in Table 3.27, following which hypotheses 43 to

51 are discussed. Based on the Hosmer-Lemeshow statistic ($p > 0.05$), as well as the overall model chi-square ($p < 0.001$), the model presented an acceptable fit

Table 3.27: Logistic Regression Analysis to Assess Predictors of Lipid Monitoring Within Three Months of a Change in Statin Dose

Variables	B	S.E.	Wald	df	Sig	Odds Ratio	95.0% Confidence Interval for Odds Ratio	
							Lower	Upper
Age at index date	-.007	.008	.796	1	.372	.993	.978	1.008
Gender (Male)[a]	.031	.146	.044	1	.834	1.031	.775	1.372
Ethnicity (Black, non-Hispanic)[b]	-.096	.196	.241	1	.623	.908	.619	1.334
Ethnicity (Hispanic)[b]	.105	.155	.460	1	.498	1.111	.820	1.505
Ethnicity (American Indian or Alaskan/Asian or Pacific Islander)[b]	-.472	.548	.742	1	.389	.624	.213	1.826
Diabetes prior to index date[c]	.253	.143	3.112	1	.078	1.288	.972	1.706
Hypertension prior to index date[d]	-.117	.151	.606	1	.436	.889	.662	1.195
CHD prior to index date[e]	-.181	.176	1.057	1	.304	.835	.591	1.178
Atherosclerosis prior to index date[f]	.359	.189	3.621	1	.057	1.432	.989	2.073
Physician specialty (Family practice/general practice)[g]	-.323	.309	1.092	1	.296	.724	.395	1.327
Physician specialty (Internal medicine)[g]	-.206	.308	.445	1	.505	.814	.445	1.490
Physician specialty (Others)[g]	-.211	.338	.391	1	.532	.809	.417	1.570
Lipid test three months prior to index date[h]	1.352	.150	81.425	1	.000*	3.865	2.881	5.183

Hosmer and Lemeshow Goodness of fit test: Chi-square = 6.377; df = 8; p = 0.605; Model Chi-square = 108.127; df = 13; p < 0.001; ***p < 0.05**
N = 1,740; [a]Reference category is female.
[b]Reference category is whites, non-Hispanic.
[c]Reference category is absence of diabetes.
[d]Reference category is absence of hypertension.
[e]Reference category is absence of CHD.
[f]Reference category is absence of atherosclerosis.
[g]Reference category is cardiologists.
[h]Reference category is absence of lipid test.

Hypothesis 43: The likelihood of a lipid test after an initial change in statin dose will be higher for males than for females controlling for age, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.

Based on the results of the logistic regression analysis presented in Table 3.27, the likelihood of lipid test did not differ by gender (OR = 1.031; 95% CI: 0.775-1.372; p = 0.834), controlling for age, ethnicity, disease conditions, physician specialty, and lipid monitoring at baseline. Thus, hypothesis 43 was rejected.

Hypothesis 44: The likelihood of a lipid test after an initial change in statin dose will be higher for older patients than for younger patients, controlling for ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.

Based on the results of the logistic regression analysis presented in Table 3.27, the likelihood of lipid test did not differ by age (OR = 0.993; 95% CI: 0.978-1.008; p = 0.372), controlling for age, ethnicity, disease conditions, physician specialty, and lipid monitoring at baseline. Thus, hypothesis 44 was rejected.

Hypothesis 45: The likelihood of a lipid test after an initial change in statin dose will be higher for non-Hispanic whites than for other ethnic groups, controlling for age, gender, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.

Based on the results of the logistic regression analysis presented in Table 3.27, the likelihood of lipid test for non-Hispanic whites did not differ from non-Hispanic blacks (OR = 0.908; 95% CI: 0.619-1.334; p = 0.623), and Hispanics (OR = 1.111; 95% CI:

0.820-1.505; p = 0.498). Although statistically non-significant (p = 0.389), the odds of American Indian/Alaskan or Asian/Pacific Islander receiving a test was lower as compared to non-Hispanic whites (OR = 0.624; 95% CI: 0.213-1.826), controlling for age, gender, disease conditions, physician specialty, and lipid monitoring at baseline. Thus, hypothesis 45 was rejected.

Hypothesis 46: The likelihood of a lipid test after an initial change in statin dose will be higher for patients with CHD than for those without CHD, controlling for age, gender, ethnicity, presence of diabetes, hypertension, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.

Based on the results of the logistic regression analysis presented in Table 3.27, there was no difference in the likelihood of lipid tests between CHD and non-CHD patients (OR = 0.835; 95% CI: 0.591-1.178; p = 0.304), controlling for demographic characteristics, other disease conditions, physician specialty and lipid monitoring at baseline. Thus, hypothesis 46 was rejected.

Hypothesis 47: The likelihood of a lipid test after an initial change in statin dose will be higher for patients with diabetes than for those without diabetes, controlling for age, gender, ethnicity, presence of CHD, hypertension, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.

Based on the results of the logistic regression analysis presented in Table 3.27, the likelihood of a lipid test after an initial change in statin type was 1.3 times higher for diabetics compared to non-diabetics (OR = 1.288; 95% CI: 0.972-1.706), controlling for demographic characteristics, other disease conditions, physician specialty and lipid

testing prior to index date. However, the result was not statistically significant (p = 0.078). Thus, hypothesis 47 was rejected.

Hypothesis 48: The likelihood of a lipid test after an initial change in statin dose will be higher for patients with hypertension than for those without hypertension, controlling for age, gender, ethnicity, presence of CHD, diabetes, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.

Based on the results of the logistic regression analysis presented in Table 3.27, the likelihood of a lipid test after an initial change in statin type did not differ significantly between hypertensives versus non-hypertensives (OR = 0.889; 95% CI: 0.662-1.195; p = 0.436), controlling for demographic characteristics, other disease conditions, physician specialty, and lipid testing prior to index date. Thus, hypothesis 48 was rejected.

Hypothesis 49: The likelihood of a lipid test after an initial change in statin dose will be higher for patients with atherosclerotic diseases than for those without atherosclerotic diseases, controlling for age, gender, ethnicity, presence of CHD, diabetes, and hypertension, physician specialty and lipid testing prior to index date.

Based on the results of the logistic regression analysis presented in Table 3.27, patients with atherosclerotic diseases had a 1.4 times greater likelihood of receiving a lipid test following an initial change in statin dose compared to those patients without atherosclerotic diseases (OR = 1.432; 95% CI: 0.989-2.073), controlling for demographic characteristics, other disease conditions, physician specialty and lipid testing prior to index date. However, the result was statistically non-significant (p = 0.057). Thus, hypothesis 49 was rejected.

Hypothesis 50: The likelihood of a lipid test after an initial change in statin type will be higher for patients treated by a cardiologist at index date than for those treated by other physician specialty, controlling for age, gender, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, and lipid testing prior to index date.

*Ba*sed on the results of the logistic regression analysis presented in Table 3.27, the likelihood of lipid testing was slightly lower among those patients treated by family practice/general practice physicians (OR = 0.724; 95% CI: 0.395-1.327; p = 0.296), physicians with specialization in internal medicine (OR = 0.814; 95% CI: 0.445-1.490; p = 0.505) and those with other specialties (OR = 0.809; 95% CI: 0.417-1.570; p = 0.532) compared to cardiologists. However, the results were statistically non-significant. Thus, hypothesis 50 was rejected.

Hypothesis 51: The likelihood of a lipid test after an initial change in statin type will be higher for patients with lipid tests at baseline than those without lipid tests at baseline, controlling for age, gender, ethnicity, presence of CHD, diabetes, and hypertension, atherosclerotic diseases, and physician specialty.

Based on the results of the logistic regression analysis presented in Table 3.27, the presence of a lipid test prior to the index date was a significant predictor for lipid monitoring after the initial change in statin dose. Patients who had a lipid test prior to the start of therapy were 3.8 times more likely to get a lipid test after the change in statin type (OR = 3.865; 95% CI: 2.881-5.183; $p < 0.001$), controlling for other variables. Thus, hypothesis 51 was not rejected.

Objective 20: To assess the predictors of the occurrence of LFTs at baseline (within three months prior to start of therapy).

Presence of liver function tests (LFTs) was assessed within three months (but not earlier than six weeks) prior to the start of statin therapy. The dependent variable LFT was coded as 1 = presence of an LFT; and 0 = no LFT. Hypotheses 52 to 58 that addressed this study objective were tested using logistic regression analysis. The predictor variables included age, gender, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic disease as well as physician specialty at index date as the predictor variables.

The following logistic regression model was used to assess predictors of LFT at baseline:

$\ln(OR) = \alpha + \beta_1$ age $+ \beta_2$ gender $+ \beta_3$ ethnicity $+ \beta_4$ CHD $+ \beta_5$ diabetes $+ \beta_6$ hypertension $+ \beta_7$ atherosclerotic disease $+ \varepsilon$

ln(OR) = overall logit of the likelihood of a LFT at baseline.

β_i (i=1,2,3,4,5,6,7)= coefficient for the change in ln(OR) associated with a one unit change in gender, ethnicity, type of CHD prevention, presence of diabetes as a risk factor, presence of hypertension as a risk factor, and presence of atherosclerotic disease,

α = intercept

ε = error term

Younger age, being female and being diabetic or hypertensive was associated with the increased likelihood of an LFT prior to start of therapy, controlling for other variables. The results of the logistic regression analysis are presented in Table 3.28,

following which hypotheses 49 to 55 are discussed. Based on the Hosmer-Lemeshow statistic ($p > 0.05$) as well as overall model chi-square ($p < 0.001$), the model presented an acceptable fit.

Table 3.28: Logistic Regression Analysis to Assess Predictors of Liver Function Tests (LFT) Within Three Months Prior to Start of Statin Therapy

Variables	B	S.E.	Wald	df	Sig	Odds Ratio	95.0% Confidence Interval for Odds Ratio	
							Lower	Upper
Age at index date	-.010	.004	7.063	1	.008*	.990	.982	.997
Gender (Male)[a]	-.212	.074	8.268	1	.004*	.809	.700	.935
Ethnicity (Black, non-Hispanic)[b]	-.156	.091	2.892	1	.089	.856	.715	1.024
Ethnicity (Hispanic)[b]	.115	.079	2.150	1	.143	1.122	.962	1.309
Ethnicity (American Indian or Alaskan)[b]	-.792	.738	1.151	1	.283	.453	.107	1.925
Ethnicity (Asian or Pacific Islander)[b]	-.297	.311	.912	1	.340	.743	.404	1.366
Diabetes prior to index date[c]	.275	.071	14.971	1	.000*	1.316	1.145	1.513
Hypertension prior to index date[d]	.570	.076	55.543	1	.000*	1.768	1.522	2.054
CHD prior to index date[e]	-.059	.081	.530	1	.467	.943	.804	1.105
Atherosclerosis prior to index date[f]	.044	.098	.206	1	.650	1.045	.863	1.266

Hosmer and Lemeshow Goodness of fit test: Chi-square = 4.437; df = 8; p = 0.816; Model Chi-square = 113.460; df = 10; p < 0.001

***p < 0.05**

N = 7,054

[a]Reference category is female.

[b]Reference category is white, non-Hispanic.

[c]Reference category is absence of diabetes.

[d]Reference category is absence of hypertension.

[e]Reference category is absence of CHD.

[f]Reference category is absence of atherosclerosis.

Hypothesis 52: The likelihood of an LFT at baseline will be higher for males than for females, controlling for age, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases.

Based on the results of the logistic regression analysis presented in Table 3.28, males (OR = 0.809; 95% CI: 0.700-0.935; p = 0.004) were associated with decreased odds of getting an LFT as compared to females, controlling for age, ethnicity, and disease conditions . Thus, hypothesis 52 was rejected.

Hypothesis 53: The likelihood of an LFT at baseline will be higher for older patients than for younger patients, controlling for gender, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases.

Based on the results of the logistic regression analysis presented in Table 3.28, older age (OR = 0.990; 95% CI: 0.982-0.997; p = 0.008) was associated with a slight but significant decrease in the odds of getting an LFT compared to younger patients, controlling for gender, ethnicity, and presence of disease conditions. Thus, hypothesis 53 was rejected.

Hypothesis 54: The likelihood of an LFT at baseline will be higher for non-Hispanic whites than for other ethnic groups, controlling for age, gender, presence of CHD, diabetes, hypertension, and atherosclerotic diseases.

Based on the results of the logistic regression analysis presented in Table 3.28, the odds of an LFT at baseline did not differ significantly between non-Hispanic whites and non-Hispanic blacks (OR = 0.856; 95% CI: 0.715-1.024; p = 0.089) or Hispanics (OR = 1.122; 95% CI: 0.962-1.309; p = 0.143). Though statistically non-significant (p = 0.283), American Indian or Alaskans had a decreased likelihood of LFT at baseline (OR = 0.453;

95% CI: 0.107-1.925) compared to non-Hispanic whites, controlling for age, gender, and disease conditions. Thus, hypothesis 54 was rejected.

Hypothesis 55: The likelihood of an LFT at baseline will be higher for patients with CHD than for those without CHD, controlling for age, gender, ethnicity, presence of diabetes, hypertension, and atherosclerotic diseases.

Based on the results of the logistic regression analysis presented in Table 3.28, the odds of an LFT at baseline did not differ significantly between those patients with and without a prior diagnosis for CHD (OR = 0.943; 95% CI: 0.804-1.105; p = 0.467), controlling for demographic characteristics, and other disease conditions. Thus, hypothesis 55 was rejected.

Hypothesis 56: The likelihood of an LFT at baseline will be higher for patients with diabetes than for those without diabetes, controlling for age, gender, ethnicity, presence of CHD, hypertension, and atherosclerotic diseases.

Based on the results of the logistic regression analysis presented in Table 3.28, patients with diabetes (OR = 1.316; 95% CI: 1.145-1.513; p < 0.001) had a greater likelihood of having an LFT compared to those without diabetes, controlling for demographic characteristics, and other disease conditions. Thus, hypothesis 56 was not rejected.

Hypothesis 57: The likelihood of an LFT at baseline will be higher for patients with hypertension than those without hypertension, controlling for age, gender, ethnicity, presence of CHD, diabetes, and atherosclerotic diseases.

Based on the results of the logistic regression analysis presented in Table 3.28, patients with hypertension (OR = 1.768; 95% CI: 1.522-2.054; $p < 0.001$) in the year prior to the index date had a higher likelihood of having an LFT compared to those without hypertension, controlling for demographic characteristics and other disease conditions. Thus, hypothesis 57 was not rejected.

Hypothesis 58: The likelihood of an LFT at baseline will be higher for patients with atherosclerotic diseases than those without atherosclerotic diseases, controlling for age, gender, ethnicity, presence of CHD, diabetes, and hypertension.

Based on the results of the logistic regression analysis presented in Table 3.28, there was no significant difference in the likelihood of an LFT between those patients with atherosclerotic diseases versus those without (OR = 1.045; 95% CI: 0.863-1.266; $p = 0.650$), controlling for demographic characteristics, and other disease conditions. Thus, hypothesis 58 was rejected.

Objective 21: To assess the predictors of the occurrence of LFTs (within three months, but not earlier than six weeks) after the start of therapy.

Presence of liver function tests (LFTs) was assessed within three months (but not earlier than six weeks) from the start of statin therapy. The dependent variable LFT was coded as 1 = presence of a LFT; and 0 = no LFT. Hypotheses 59 to 67 addressing this

study objective were tested using logistic regression analysis with age, gender, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic disease, physician specialty at index date, and LFT prior to start of therapy as the predictor variables in the model.

The following logistic regression model was used to assess predictors of LFTs after start of therapy:

$\ln(OR) = \alpha + \beta_1$ age $+ \beta_2$ gender $+ \beta_3$ ethnicity $+ \beta_4$ CHD $+ \beta_5$ diabetes $+ \beta_6$ hypertension $+ \beta_7$ atherosclerotic disease $+ \beta_8$ physician specialty at index date $+ \beta_9$ prior LFT $+ \varepsilon$

where:

ln(OR) = overall logit of the likelihood of LFT after start of therapy.

β_i (i=1,2,3,4,5,6,7,8,9)= coefficient for the change in ln(OR) associated with a one unit change in gender, ethnicity, type of CHD prevention, presence of diabetes as a risk factor, presence of hypertension as a risk factor, presence of atherosclerotic disease, physician specialty, and presence of LFT at baseline.

α = intercept ; ε = error term

Older age and being non-Hispanic black was associated with a decreased likelihood of the presence of LFTs than being younger and non-Hispanic whites, controlling for other variables. However, patients with hypertension and those with prior LFTs were more likely to have their LFTs after start of therapy. The results of the logistic regression analysis are presented in Table 3.29, following which hypotheses 59 to 67 are discussed. Based on the Hosmer-Lemeshow statistic ($p > 0.05$), as well as overall model chi-square ($p < 0.001$), the model presented an acceptable fit.

Table 3.29: Logistic Regression Analysis to Assess Predictors of Liver Function Tests (LFTs) within Three Months From the Start of Statin Therapy

Variables	B	S.E.	Wald	df	Sig	Odds Ratio	95.0% Confidence Interval for Odds Ratio	
							Lower	Upper
Age at index date	-.013	.005	6.885	1	.009*	.987	.977	.997
Gender (Male)[a]	-.071	.095	.560	1	.454	.931	.772	1.122
Ethnicity (Black, non-Hispanic)[b]	-.611	.139	19.263	1	.000*	.543	.413	.713
Ethnicity (Hispanic)[b]	.016	.099	.026	1	.872	1.016	.836	1.235
Ethnicity (American Indian or Alaskan)[b]	-.830	1.030	.649	1	.421	.436	.058	3.286
Ethnicity (Asian or Pacific Islander)[b]	-.186	.379	.240	1	.624	.831	.396	1.744
Diabetes prior to index date[c]	.012	.095	.015	1	.901	1.012	.840	1.218
Hypertension prior to index date[d]	.271	.099	7.527	1	.006*	1.312	1.081	1.592
CHD prior to index date[e]	.157	.112	1.963	1	.161	1.170	.939	1.456
Atherosclerosis prior to index date[f]	.074	.128	.332	1	.565	1.076	.838	1.383
Specialty (Family practice/general practice)[g]	-.118	.183	.414	1	.520	.889	.621	1.272
Specialty (Internal medicine)[g]	.120	.181	.440	1	.507	1.127	.791	1.607
Specialty (Other)[g]	-.052	.203	.065	1	.799	.950	.638	1.414
LFT three months prior to index date[f]	1.270	.098	168.280	1	.000*	3.561	2.939	4.315

Hosmer and Lemeshow Goodness of fit test: Chi-square = 2.996; df = 8; p = 0.935; Model Chi-square = 213.648.; df = 14; p < 0.001

N = 6,203; ***p < 0.05**

[a]Reference category is female.

[b]Reference category is white, non-Hispanic.

[c]Reference category is absence of diabetes.

[d]Reference category is absence of hypertension.

[e]Reference category is absence of CHD.

[f]Reference category is absence of atherosclerosis.

[g]Reference category is cardiologists.

[f]Reference category is absence of liver function test.

Hypothesis 59: The likelihood of an LFT after start of therapy will be higher for males than for females controlling for age, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, physician specialty, and presence of LFT prior to index date.

Based on the results of the logistic regression analysis presented in Table 3.29, the likelihood of a LFT after start of therapy did not differ significantly with respect to gender (OR = 0.931; 95% CI: 0.772-1.122; p = 0.454), controlling for age, ethnicity, disease conditions, physician specialty, and presence of LFT prior to index date. Thus, hypothesis 59 was rejected.

Hypothesis 60: The likelihood of an LFT after start of therapy will be higher for older patients than for younger ones, controlling for gender, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, physician specialty, and presence of LFT prior to index date.

Based on the results of the logistic regression analysis presented in Table 3.29, the there was a slight decrease in the likelihood of an LFT after start of therapy with an increase in age (OR = 0.987, 95% CI: 0.977-0.997, p = 0.009), controlling for gender, ethnicity, disease conditions, and physician specialty. Thus, hypothesis 60 was rejected.

Hypothesis 61: The likelihood of an LFT after start of therapy will be higher for non-Hispanic whites than for other ethnic groups, controlling for age, gender, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, physician specialty and presence of LFT prior to index date.

Based on the results of the logistic regression analysis presented in Table 3.29, non-Hispanic blacks had a decreased likelihood of getting LFTs compared to non-Hispanic whites (OR = 0.543, 95% CI: 0.413-0.713; p < 0.001). Non-Hispanic whites

did not have a greater likelihood of getting an LFT compared to Hispanics (OR = 1.016; 95% CI: 0.836-1.235; p = 0.872). American Indians or Alaskan had a decreased odd of receiving an LFT compared to non-Hispanic whites (OR = 0.436), though the result was non-significant (p = 0.421) and the confidence interval for the odds ratio was large (95% CI: 0.058-3.286). The likelihood of receiving an LFT did not differ significantly between non-Hispanic whites and Asians or Pacific Islanders (OR = 0.831; 95% CI: 0.396-1.744; p = 0.624). Based on the results, hypothesis 61 was rejected.

Hypothesis 62: The likelihood of an LFT after start of therapy will be higher for patients with CHD than for those without CHD, controlling for age, gender, ethnicity, presence of diabetes, hypertension, and atherosclerotic diseases, physician specialty, and presence of LFT prior to index date.

Based on the results of the logistic regression analysis presented in Table 3.29, patients with a diagnosis of CHD at or a year prior to the index date did not have a greater likelihood of an LFT at the start of therapy than those without CHD (OR = 1.170; 95% CI: 0.939-1.456; p = 0.161), controlling for demographic characteristics, other disease conditions, physician specialty, and LFT prior to index date. Thus, hypothesis 62 was rejected.

Hypothesis 63: The likelihood of an LFT after start of therapy will be higher for patients with diabetes than for those without diabetes, controlling for age, gender, ethnicity, presence of CHD, hypertension, and atherosclerotic diseases, physician specialty, and presence of LFT prior to index date.

Based on the results of the logistic regression analysis presented in Table 3.29, the odds of receiving an LFT between those patients with a diagnosis of diabetes and those

without did not differ significantly from one (OR = 1.012; 95% CI: 0.840-1.218; p = 0.901), controlling for demographic characteristics, other disease conditions, physician specialty, and presence of LFT prior to index date. Thus, hypothesis 63 was rejected.

Hypothesis 64: The likelihood of an LFT after start of therapy will be higher for patients with hypertension than for those without hypertension, controlling for age, gender, ethnicity, presence of CHD, diabetes, and atherosclerotic diseases, physician specialty and presence of LFT to index date.

Based on the results of the logistic regression analysis presented in Table 3.29, patients with a diagnosis for hypertension were 1.3 times more likely to receive an LFT compared to those without a diagnosis for hypertension (OR = 1.312; 95% CI: 1.081-1.592; p = 0.006), controlling for demographic characteristics, other disease conditions, physician specialty, and presence of LFT prior to index date. Thus, hypothesis 64 was not rejected.

Hypothesis 65: The likelihood of an LFT after start of therapy will be higher for patients with atherosclerotic diseases than for those without atherosclerotic diseases, controlling for age, gender, ethnicity, presence of CHD, diabetes, and hypertension, physician specialty, and presence of LFT prior to index date.

Based on the results of the logistic regression analysis presented in Table 3.29, the odds of receiving an LFT did not differ significantly between those patients with atherosclerotic diseases and those without, controlling for demographic characteristics, other disease conditions, physician specialty, and presence of LFT prior to index date (OR = 1.076; 95% CI: 0.838-1.383; p = 0.565). Thus, hypothesis 65 was rejected.

Hypothesis 66: The likelihood of an LFT at start of therapy will be higher for patients treated by a cardiologist at index date than for those treated by other physician specialty, controlling for age, gender, ethnicity, presence of CHD, diabetes, hypertension and atherosclerotic diseases, and presence of LFT prior to index date.

Based on the results of the logistic regression analysis presented in Table 3.29, the likelihood of an LFT at the start of therapy did not differ significantly for those patients treated by a cardiologist at index date compared to family practice/general practice (OR = 0.889; 95% CI: 0.621-1.272; p = 0.520), internal medicine (OR = 1.127; 95% CI: 0.791-1.607; p = 0.507) or other physician specialty (OR = 0.950; 95% CI: 0.638-1.414; p = 0.799). Thus, hypothesis 66 was rejected.

Hypothesis 67: The likelihood of an LFT after start of therapy will be higher for patients with LFTs at baseline than those without LFTs at baseline, controlling for age, gender, ethnicity, presence of CHD, diabetes, and hypertension, atherosclerotic diseases, and physician specialty.

Based on the results of the logistic regression analysis presented in Table 3.29, the presence of an LFT prior to the index date was a significant predictor of LFTs after the start of therapy. Patients who had an LFT prior to the start of therapy were 3.6 times more likely to get an LFT after the start of therapy (OR = 3.561; 95% CI: 2.939-4.315; p < 0.001). Thus, hypothesis 67 was not rejected.

Objective 22: To assess the predictors of the occurrence of LFTs (within three months, but not earlier than six weeks) following the initial increase in statin dose.

Presence of liver function tests (LFTs) was assessed within three months (but not earlier than six weeks) of an increase in statin dose. The dependent variable LFT was coded as 1= presence of an LFT; and 0 = no LFT. Hypotheses 68 to 76, addressing this study objective were tested using a logistic regression analysis with age, gender, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic disease, physician specialty at index date, and presence of LFT prior to start of therapy as the predictor variables in the model.

The following logistic regression model was used to assess predictors of LFTs after an increase in statin dose:

$\ln(OR) = \alpha + \beta_1$ age $+ \beta_2$ gender $+ \beta_3$ ethnicity $+ \beta_4$ CHD $+ \beta_5$ diabetes $+ \beta_6$ hypertension $+ \beta_7$ atherosclerotic disease $+ \beta_8$ physician specialty at index date $+ \beta_9$ prior lipid test $+ \varepsilon$

ln(OR) = overall logit of the likelihood of LFT after increase in statin dose.

β_i (i=1,2,3,4,5,6,7,8,9)= coefficient for the change in ln(OR) associated with a one unit change in gender, ethnicity, type of CHD prevention, presence of diabetes as a risk factor, presence of hypertension as a risk factor, presence of atherosclerotic disease, physician specialty, and presence of LFT at baseline.

α = intercept

ε = error term

Being treated by a cardiologist at index date, presence of CHD prior to index date, and having a prior LFT were significant predictors of the likelihood of LFT after an increase in statin dose, controlling for other variables. The results of the logistic regression analysis are presented in Table 3.30, following which the study hypotheses 68 to 76 are discussed. Based on the Hosmer-Lemeshow statistic ($p > 0.05$), as well as overall model chi-square ($p < 0.001$), the model presented an acceptable fit.

Table 3.30: Logistic Regression to Assess Predictors of Liver Function Tests Within Three Months Following an Increase in Dose

Variables	B	S.E.	Wald	df	Sig	Odds Ratio	95.0% Confidence Interval for Odds Ratio	
							Lower	Upper
Age at index date	.006	.010	.332	1	.564	1.006	.986	1.026
Gender (Male)[a]	.066	.185	.127	1	.722	1.068	.744	1.534
Ethnicity (Black, non-Hispanic)[b]	-.309	.747	.171	1	.679	.734	.170	3.175
Ethnicity (Hispanic)[b]	.310	.195	2.526	1	.112	1.364	.930	2.000
Ethnicity (American Indian or Alaskan/Asian or Pacific Islander)[b]	-.145	.259	.316	1	.574	.865	.520	1.436
Diabetes prior to index date[c]	.097	.184	.281	1	.596	1.102	.769	1.579
Hypertension prior to index date[d]	.053	.189	.080	1	.777	1.055	.729	1.527
CHD prior to index date[e]	-.471	.239	3.862	1	.049	.625	.391	.999
Atherosclerosis prior to index date[f]	-.202	.271	.556	1	.456	.817	.481	1.389
Specialty (Family practice/general practice)[g]	-1.065	.347	9.425	1	.002*	.345	.175	.680
Specialty (Internal medicine)[g]	-.791	.342	5.346	1	.021*	.453	.232	.886
Specialty (Other)[g]	-.535	.375	2.044	1	.153	.585	.281	1.220
LFT three months prior to index date[f]	1.084	.191	32.174	1	.000*	2.956	2.033	4.299

Hosmer and Lemeshow Goodness of fit test: Chi-square = 9.256; df = 8; p = 0.321; Model Chi-square = 47.888; df = 13; p < 0.001

N = 1,910; ***p < 0.05**

[a]Reference category is female.

[b]Reference category is white, non-Hispanic.

[c]Reference category is absence of diabetes.

[d]Reference category is absence of hypertension.

[e]Reference category is absence of CHD.

[f]Reference category is absence of atherosclerosis.

[g]Reference category is cardiologists.

[h]Reference category is absence of liver function test.

Hypothesis 68: The likelihood of an LFT after an initial change in statin dose will be higher for males than for females controlling for age, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, physician specialty, and presence of LFT prior to index date.

Based on the results of the logistic regression analysis presented in Table 3.30, the likelihood of an LFT did not differ by gender (OR = 1.068; 95% CI: 0.744-1.534; p = 0.722), controlling for age, ethnicity, disease conditions, physician specialty, and presence of LFT at baseline. Thus, hypothesis 68 was rejected.

Hypothesis 69: The likelihood of an LFT after an initial increase in statin dose will be higher for older patients than for younger patients, controlling for gender, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, physician specialty, and presence of LFT prior to index date.

Based on the results of the logistic regression analysis presented in Table 3.30, the likelihood of LFT did not differ by age (OR = 1.006; 95% CI: 0.986-1.026; p = 0.564), controlling for ethnicity, gender, disease conditions, physician specialty, and presence of LFT at baseline. Thus, hypothesis 69 was rejected.

Hypothesis 70: The likelihood of an LFT after initial increase in statin dose will be higher for non-Hispanic whites than for other ethnic groups, controlling for age, gender, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, physician specialty, and presence of LFT prior to index date.

Based on the results of the logistic regression analysis presented in Table 3.30, the likelihood of LFT for non-Hispanic whites did not differ from non-Hispanic blacks (OR = 0.734; 95% CI: 0.170-3.175; p = 0.679), Hispanics (OR = 1.364; 95% CI: 0.930-2.000; p = 0.112) and American Indians/Alaskans or Asians/Pacific Islanders

(OR = 0.865; 95% CI: 0.520-1.436; p = 0.574), controlling for age, gender, disease conditions, physician specialty, and presence of LFT at baseline. Thus, hypothesis 70 was rejected.

Hypothesis 71: The likelihood of a LFT after an initial increase in statin dose will be higher for patients with CHD than for those without CHD, controlling for age, gender, ethnicity, presence of diabetes, hypertension, and atherosclerotic diseases, physician specialty and presence of LFT prior to index date.

Based on the results of the logistic regression analysis presented in Table 3.30, the likelihood of a LFT was significantly lower among patients with CHD and than in non-CHD patients (OR = 0.625; 95% CI: 0.391-0.999; p = 0.049), controlling for demographic characteristics, other disease conditions, physician specialty, and presence of LFT at baseline. Thus, hypothesis 71 was rejected.

Hypothesis 72: The likelihood of a LFT after an initial increase in statin dose will be higher for patients with diabetes than for those without diabetes, controlling for age, gender, ethnicity, presence of CHD, hypertension, and atherosclerotic diseases, physician specialty and presence of LFT prior to index date.

Based on the results of the logistic regression analysis presented in Table 3.30, the likelihood of a LFT after an initial increase in statin dose did not differ significantly between diabetics and non-diabetics (OR = 1.102; 95% CI: 0.769-1.579; p = 0.596), controlling for demographic characteristics, other disease conditions, physician specialty, and presence of LFT prior to index date. Thus, hypothesis 72 was rejected.

Hypothesis 73: The likelihood of a LFT after an initial increase in statin dose will be higher for patients with hypertension than for those without hypertension, controlling for age, gender, ethnicity, presence of CHD, diabetes, and atherosclerotic diseases, physician specialty, and presence of LFT prior to index date.

Based on the results of the logistic regression analysis presented in Table 3.30, the likelihood of a *LFT* after an initial change in statin type did not differ significantly between hypertensives versus non-hypertensives (OR = 1.055; 95% CI: 0.729-1.527; p = 0.777), controlling for demographic characteristics, other disease conditions, physician specialty and presence of LFT prior to index date. Thus, hypothesis 73 was rejected.

Hypothesis 74: The likelihood of a LFT after an initial increase in statin dose will be higher for patients with atherosclerotic diseases than for those without atherosclerotic diseases, controlling for age, gender, ethnicity, presence of CHD, diabetes, and hypertension, physician specialty, and lipid testing prior to index date.

Based on the results of the logistic regression analysis presented in Table 3.30, the likelihood of a *LFT* after an initial change in statin type did not differ significantly between those with atherosclerotic diseases versus those without (OR = 0.817; 95% CI: 0.481-1.389; p = 0.456), controlling for demographic characteristics, other disease conditions, physician specialty, and presence of LFT prior to index date. Thus, hypothesis 74 was rejected.

Hypothesis 75: The likelihood of a LFT after an initial increase in statin dose will be higher for patients treated by a cardiologist at index date than for those treated by other physician specialty, controlling for age, gender, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, and presence of LFT prior to index date

Based on the results of the logistic regression analysis presented in Table 3.30, the likelihood of LFT was lower among those patients treated by family practice/general practice physicians (OR = 0.345; 95% CI: 0.175-0.680; p = 0.002), physicians with specialization in internal medicine (OR = 0.453; 95% CI: 0.232-0.886; p = 0.021) and those with other specialties (OR = 0.585; 95% CI: 0.281-1.220) compared to cardiologists. However, the results for the "other specialty" group were not significant (p = 0.153). Thus, hypothesis 75 was rejected.

Hypothesis 76: The likelihood of an LFT after an initial increase in dose will be higher for patients with LFTs at baseline than those without LFTs at baseline, controlling for age, gender, ethnicity, presence of CHD, diabetes, and hypertension, atherosclerotic diseases, and physician specialty.

Based on the results of the logistic regression analysis presented in Table 3.30, the presence of an LFT prior to the index date was a significant predictor for LFT after the initial increase in statin dose. Patients who had a LFT prior to the start of therapy were 2.9 times more likely to get an LFT after an initial increase in statin dose (OR = 2.956; 95% CI: 2.033-4.299; p < 0.001). Thus, hypothesis 76 was not rejected.

SUMMARY OF THE STUDY HYPOTHESES

Table 3.31 presents a summary of the study hypotheses and the results.

Table 3.31: Results of Hypotheses Testing

Hypothesis	Description	Rejected/Not rejected
Hypothesis 1	*The starting dose for statin therapy for secondary prevention patients will be higher than for primary prevention patients, controlling for the type of statin.*	Rejected
Hypothesis 2	*The MPR will be higher for males than for females, controlling for age, ethnicity, presence of CHD, diabetes, hypertension, atherosclerotic diseases, and total number of prescriptions.*	Not rejected
Hypothesis 3	*The MPR will be higher for older patients than for younger patients, controlling for gender, ethnicity, presence of CHD, diabetes, hypertension, atherosclerotic disease, and total number of prescriptions.*	Rejected
Hypothesis 4	*The MPR will be higher for non-Hispanic whites than for other ethnic groups, controlling for age, gender, presence of CHD, diabetes, hypertension, atherosclerotic diseases, and total number of prescriptions.*	Not rejected
Hypothesis 5	*The MPR will be higher for secondary prevention CHD patients than for primary prevention CHD patients, controlling for age, gender, ethnicity, presence of diabetes, hypertension, atherosclerotic diseases, and total number of prescriptions.*	Rejected
Hypothesis 6	*The MPR will be higher for diabetics than for non-diabetics, controlling for age, gender, ethnicity, presence of CHD, hypertension, atherosclerotic diseases, and total number of prescriptions.*	Rejected

Table 3.31: Results of Hypotheses Testing

Hypothesis	Description	Rejected/Not rejected
Hypothesis 7	*The MPR will be higher for hypertensives than for non-hypertensives, controlling for age, gender, ethnicity, presence of CHD, diabetes, atherosclerotic diseases, and total number of prescriptions.*	Rejected
Hypothesis 8	*The MPR will be higher for those patients with atherosclerotic diseases than for those without, atherosclerotic diseases, controlling for age, gender, ethnicity, presence of CHD, diabetes, hypertension, and total number of prescriptions.*	Rejected
Hypothesis 9	*The MPR will be higher for those patients on a lower number of total prescriptions other than statins than for those on a higher number of prescriptions, controlling for age, gender, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic disease.*	Rejected
Hypothesis 10	*Females will have a higher hazard of becoming non-persistent to statin therapy than males controlling for age, ethnicity, presence of CHD, hypertension, diabetes, atherosclerotic diseases, and total number of prescriptions.*	Not rejected
Hypothesis 11	*Younger patients will have a higher hazard of becoming non-persistent to statin therapy than older patients, controlling for gender, ethnicity, presence of CHD, hypertension, diabetes, atherosclerotic diseases, and total number of prescriptions.*	Rejected
Hypothesis 12	*Other ethnic minorities will have a higher hazard of becoming non-persistent to statin therapy than non-Hispanic whites, controlling for age, gender, presence of CHD, hypertension, diabetes, atherosclerotic diseases, and total number of prescriptions.*	Not Rejected

Table 3.31: Results of Hypotheses Testing

Hypothesis	Description	Rejected/Not rejected
Hypothesis 13	*Patients without CHD will have a higher hazard of becoming non-persistent to statin therapy than those with CHD, controlling for age, gender, ethnicity, presence of hypertension, diabetes, atherosclerotic diseases, and total number of prescriptions.*	Rejected
Hypothesis 14	*Patients without diabetes will have a higher hazard of becoming non-persistent to statin therapy than those with diabetes, controlling for age, gender, ethnicity, presence of CHD, hypertension, atherosclerotic diseases, and total number of prescriptions.*	Rejected
Hypothesis 15	*Patients without hypertension will have a higher hazard of becoming non-persistent to statin therapy than those with hypertension, controlling for age, gender, ethnicity, presence of CHD, diabetes, atherosclerotic diseases, and total number of prescriptions.*	Rejected
Hypothesis 16	*Patients without atherosclerotic diseases will have a higher hazard of becoming non-persistent to statin therapy than those with atherosclerotic diseases controlling for age, gender, ethnicity, presence of CHD, diabetes, hypertension, and total number of prescriptions.*	Not rejected
Hypothesis 17	*Patients on greater number of total prescriptions other than statins will have a higher hazard of becoming non-persistent than those on fewer prescription, controlling for age, gender, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases.*	Rejected
Hypothesis 18	*The likelihood of a lipid test at baseline will be higher for males than for females, controlling for age, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases.*	Rejected

Table 3.31: Results of Hypotheses Testing

Hypothesis	Description	Rejected/Not rejected
Hypothesis 19	*The likelihood of a lipid test at baseline will be higher for older patients than for younger patients, controlling for gender, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases.*	Rejected
Hypothesis 20	*The likelihood of a lipid test at baseline will be higher for non-Hispanic whites than for other ethnic groups, controlling for age, gender, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases.*	Rejected
Hypothesis 21	*The likelihood of a lipid test at baseline will be higher for patients with CHD than for those without CHD, controlling for age, gender, ethnicity, presence of diabetes, hypertension, and atherosclerotic diseases.*	Rejected
Hypothesis 22	*The likelihood of a lipid test at baseline will be higher for patients with diabetes than for those without diabetes, controlling for age, gender, ethnicity, presence of CHD, hypertension, and atherosclerotic diseases.*	Not rejected
Hypothesis 23	*The likelihood of a lipid test at baseline will be higher for patients with hypertension than for those without hypertension, controlling for age, gender, ethnicity, presence of CHD, diabetes, and atherosclerotic diseases.*	Not rejected
Hypothesis 24	*The likelihood of a lipid test at baseline will be higher for patients with atherosclerotic diseases than those without atherosclerotic diseases, controlling for age, gender, ethnicity, presence of CHD, diabetes, and hypertension.*	Rejected
Hypothesis 25	*The likelihood of a lipid test at start of therapy will be higher for males than for females controlling for age, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.*	Rejected

Table 3.31: Results of Hypotheses Testing

Hypothesis	Description	Rejected/Not rejected
Hypothesis 26	*The likelihood of a lipid test at start of therapy will be higher for older patients than for younger patients, controlling for gender, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.*	Rejected
Hypothesis 27	*The likelihood of a lipid test at start of therapy will be higher for non-Hispanic whites than for other ethnic groups, controlling for age, gender, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.*	Rejected
Hypothesis 28	*The likelihood of a lipid test at start of therapy will be higher for patients with CHD than for those without CHD, controlling for age, gender, ethnicity, presence of diabetes, hypertension, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.*	Not rejected
Hypothesis 29	*The likelihood of a lipid test at start of therapy will be higher for patients with diabetes than for those without diabetes, controlling for age, gender, ethnicity, presence of CHD, hypertension, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.*	Rejected
Hypothesis 30	*The likelihood of a lipid test at start of therapy will be higher for patients with hypertension than for those without hypertension, controlling for age, gender, ethnicity, presence of CHD, diabetes, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.*	Rejected

Table 3.31: Results of Hypotheses Testing

Hypothesis	Description	Rejected/Not rejected
Hypothesis 31	*The likelihood of a lipid test at start of therapy will be higher for patients with atherosclerotic diseases than for those without atherosclerotic diseases, controlling for age, gender, ethnicity, presence of CHD, diabetes, and hypertension, physician specialty, and lipid testing prior to index date.*	Rejected
Hypothesis 32	*The likelihood of a lipid test at start of therapy will be higher for patients treated by a cardiologist at index date than for those treated by other physician specialty, controlling for age, gender, ethnicity, presence of CHD, diabetes, hypertension and atherosclerotic diseases, and lipid testing prior to index date.*	Rejected
Hypothesis 33	*The likelihood of a lipid test after start of therapy will be higher for patients with lipid tests at baseline than those without lipid tests at baseline, controlling for age, gender, ethnicity, presence of CHD, diabetes, and hypertension, atherosclerotic diseases, and physician specialty.*	Not rejected
Hypothesis 34	*The likelihood of a lipid test after an initial change in statin type will be higher for males than for females controlling for age, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.*	Rejected
Hypothesis 35	*The likelihood of a lipid test after an initial change in statin type will be higher for older patients than for younger patients, controlling for age, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.*	Rejected
Hypothesis 36	*The likelihood of a lipid test after an initial change in statin type will be higher for non-Hispanic whites than for other ethnic groups, controlling for age, gender, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.*	Rejected

Table 3.31: Results of Hypotheses Testing

Hypothesis	Description	Rejected/Not rejected
Hypothesis 37	*The likelihood of a lipid test after an initial change in statin type will be higher for patients with CHD than for those without CHD, controlling for age, gender, ethnicity, presence of diabetes, hypertension, and atherosclerotic diseases, physician specialty and lipid testing prior to index date.*	Rejected
Hypothesis 38	*The likelihood of a lipid test after an initial change in statin type will be higher for patients with diabetes than for those without diabetes, controlling for age, gender, ethnicity, presence of CHD, hypertension, and atherosclerotic diseases, physician specialty and lipid testing prior to index date.*	Rejected
Hypothesis 39	*The likelihood of a lipid test after an initial change in statin type will be higher for patients with hypertension than for those without hypertension, controlling for age, gender, ethnicity, presence of CHD, diabetes, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.*	Rejected
Hypothesis 40	*The likelihood of a lipid test after an initial change in statin type will be higher for patients with atherosclerotic diseases than for those without atherosclerotic diseases, controlling for age, gender, ethnicity, presence of CHD, diabetes, and hypertension, physician specialty, and lipid testing prior to index date.*	Rejected
Hypothesis 41	*The likelihood of a lipid test after an initial change in statin type will be higher for patients treated by a cardiologist at index date than for those treated by other physician specialty, controlling for age, gender, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, and lipid testing prior to index date.*	Rejected
Hypothesis 42	*The likelihood of a lipid test after an initial change in statin type will be higher for patients with lipid tests at baseline than those without lipid tests at baseline, controlling for age, gender, ethnicity, presence of CHD, diabetes, and hypertension, atherosclerotic diseases, and physician specialty.*	Not rejected

Table 3.31: Results of Hypotheses Testing

Hypothesis	Description	Rejected/Not rejected
Hypothesis 43	*The likelihood of a lipid test after an initial change in statin dose will be higher for males than for females controlling for age, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, physician specialty, lipid testing prior to index date*	Rejected
Hypothesis 44	*The likelihood of a lipid test after an initial change in statin dose will be higher for older patients than for younger patients, controlling for ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.*	Rejected
Hypothesis 45	*The likelihood of a lipid test after an initial change in statin dose will be higher for non-Hispanic whites than for other ethnic groups, controlling for age, gender, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.*	Rejected
Hypothesis 46	*The likelihood of a lipid test after an initial change in statin dose will be higher for patients with CHD as compared to those without CHD, controlling for age, gender, ethnicity, presence of diabetes, hypertension, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.*	Rejected
Hypothesis 47	*The likelihood of a lipid test after an initial change in statin dose will be higher for patients with diabetes than for those without diabetes, controlling for age, gender, ethnicity, presence of CHD, hypertension, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.*	Rejected
Hypothesis 48	*The likelihood of a lipid test after an initial change in statin dose will be higher for patients with hypertension than for those without hypertension, controlling for age, gender, ethnicity, presence of CHD, diabetes, and atherosclerotic diseases, physician specialty, and lipid testing prior to index date.*	Rejected

Table 3.31: Results of Hypotheses Testing

Hypothesis	Description	Rejected/Not rejected
Hypothesis 49	*The likelihood of a lipid test after an initial change in statin dose will be higher for patients with atherosclerotic diseases than for those without atherosclerotic diseases, controlling for age, gender, ethnicity, presence of CHD, diabetes, and hypertension, physician specialty and lipid testing prior to index date.*	Rejected
Hypothesis 50	*The likelihood of a lipid test after an initial change in statin dose will be higher for patients treated by a cardiologist at index date than for those treated by other physician specialty, controlling for age, gender, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, and lipid testing prior to index date.*	Rejected
Hypothesis 51	*The likelihood of a lipid test after an initial change in statin dose will be higher for patients with lipid tests at baseline than those without lipid tests at baseline, controlling for age, gender, ethnicity, presence of CHD, diabetes, and hypertension, atherosclerotic diseases, and physician specialty.*	Not rejected
Hypothesis 52	*The likelihood of an LFT at baseline will be higher for males than for females, controlling for age, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases.*	Rejected
Hypothesis 53	*The likelihood of an LFT at baseline will be higher for older patients than for younger patients, controlling for gender, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases.*	Rejected
Hypothesis 54	*The likelihood of an LFT at baseline will be higher for non-Hispanic whites than for other ethnic groups, controlling for age, gender, presence of CHD, diabetes, hypertension, and atherosclerotic diseases.*	Rejected
Hypothesis 55	*The likelihood of an LFT at baseline will be higher for patients with CHD than for those without CHD, controlling for age, gender, ethnicity, presence of diabetes, hypertension, and atherosclerotic diseases.*	Rejected
Hypothesis 56	*The likelihood of an LFT at baseline will be higher for patients with diabetes than for those without, diabetes controlling for age, gender, ethnicity, presence of CHD, hypertension, and atherosclerotic diseases.*	Not rejected

Table 3.31: Results of Hypotheses Testing

Hypothesis	Description	Rejected/Not rejected
Hypothesis 57	*The likelihood of an LFT at baseline will be higher for patients with hypertension than for those without hypertension, controlling for age, gender, ethnicity, presence of CHD, diabetes, and atherosclerotic diseases.*	Not rejected
Hypothesis 58	*The likelihood of an LFT at baseline will be higher for patients with atherosclerotic diseases than for those without atherosclerotic diseases, controlling for age, gender, ethnicity, presence of CHD, diabetes, and atherosclerotic diseases.*	Rejected
Hypothesis 59	*The likelihood of an LFT at start of therapy will be higher for males than for females controlling for age, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, physician specialty, and presence of LFT prior to index date.*	Rejected
Hypothesis 60	*The likelihood of an LFT at start of therapy will be higher for older patients than for younger patients, controlling for gender, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, physician specialty, and presence of LFT prior to index date.*	Rejected
Hypothesis 61	*The likelihood of an LFT at start of therapy will be higher for non-Hispanic whites than for other ethnic groups, controlling for age, gender, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, physician specialty and presence of LFT prior to index date.*	Rejected
Hypothesis 62	*The likelihood of an LFT at start of therapy will be higher for patients with CHD than for those without CHD, controlling for age, gender, ethnicity, presence of diabetes, hypertension, and atherosclerotic diseases, physician specialty, and presence of LFT prior to index date.*	Rejected

Table 3.31: Results of Hypotheses Testing

Hypothesis	Description	Rejected/Not rejected
Hypothesis 63	*The likelihood of an LFT at start of therapy will be higher for patients with diabetes than for those without diabetes, controlling for age, gender, ethnicity, presence of CHD, hypertension, and atherosclerotic diseases, physician specialty, and presence of LFT prior to index date.*	Rejected
Hypothesis 64	*The likelihood of an LFT at start of therapy will be higher for patients with hypertension than for those without hypertension, controlling for age, gender, ethnicity, presence of CHD, diabetes, and atherosclerotic diseases, physician specialty and presence of LFT prior to index date.*	Not rejected
Hypothesis 65	*The likelihood of an LFT at start of therapy will be higher for patients with atherosclerotic diseases than for those without atherosclerotic diseases, controlling for age, gender, ethnicity, presence of CHD, diabetes, and hypertension, physician specialty, and presence of LFT prior to index date.*	Rejected
Hypothesis 66	*The likelihood of an LFT at start of therapy will be higher for patients treated with a cardiologist at index date than for those treated by other physician specialty, controlling for age, gender, ethnicity, presence of CHD, diabetes, hypertension and atherosclerotic diseases, and presence of LFT prior to index date.*	Rejected
Hypothesis 67	*The likelihood of an LFT after start of therapy will be higher for patients with LFTs at baseline than those without LFTs at baseline, controlling for age, gender, ethnicity, presence of CHD, diabetes, and hypertension, atherosclerotic diseases, and physician specialty.*	Not rejected
Hypothesis 68	*The likelihood of an LFT after an initial increase in statin dose will be higher for males than for females controlling for age, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, physician specialty, and presence of LFT prior to index date.*	Rejected

Table 3.31: Results of Hypotheses Testing

Hypothesis	Description	Rejected/Not rejected
Hypothesis 69	*The likelihood of an LFT after an initial increase in statin dose will be higher for older patients than for younger patients, controlling for ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, physician specialty, and presence of LFT prior to index date.*	Rejected
Hypothesis 70	*The likelihood of an LFT after initial increase in statin dose will be higher for non-Hispanic whites than for other ethnic groups, controlling for age, gender, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, physician specialty, and presence of LFT prior to index date.*	Rejected
Hypothesis 71	*The likelihood of an LFT after an initial increase in statin dose will be higher for patients with CHD than for those without CHD, controlling for age, gender, ethnicity, presence of diabetes, hypertension, and atherosclerotic diseases, physician specialty and presence of LFT prior to index date.*	Rejected
Hypothesis 72	*The likelihood of an LFT after an initial increase in statin dose will be higher for patients with diabetes than for those without diabetes, controlling for age, gender, ethnicity, presence of CHD, hypertension, and atherosclerotic diseases, physician specialty and presence of LFT prior to index date.*	Rejected
Hypothesis 73	*The likelihood of an LFT after an initial increase in statin dose will be higher for patients with hypertension than for those without hypertension, controlling for age, gender, ethnicity, presence of CHD, diabetes, and atherosclerotic diseases, physician specialty, and LFT prior to index date.*	Rejected

Table 3.31: Results of Hypotheses Testing

Hypothesis	Description	Rejected/Not rejected
Hypothesis 74	*The likelihood of an LFT after an initial increase in statin dose will be higher for patients with atherosclerotic diseases than for those without atherosclerotic diseases, controlling for age, gender, ethnicity, presence of CHD, diabetes, and hypertension, physician specialty, and LFT prior to index date.*	Rejected
Hypothesis 75	*The likelihood of an LFT after an initial increase in statin dose will be higher for patients treated by a cardiologist at index date than for those treated by other physician specialty, controlling for age, gender, ethnicity, presence of CHD, diabetes, hypertension, and atherosclerotic diseases, and presence of LFT prior to index date*	Rejected
Hypothesis 76	*The likelihood of an LFT after an initial increase in statin dose will be higher for patients with LFTs at baseline than those without LFTs at baseline, controlling for age, gender, ethnicity, presence of CHD, diabetes, and hypertension, atherosclerotic diseases, and physician specialty.*	Not rejected

CHAPTER 4

DISCUSSION AND CONCLUSIONS

Hyperlipidemia plays a central role in the development of atherosclerotic plaque that impairs arterial blood flow leading to arterial obstruction and myocardial infarction in coronary vessels.[438] The management of hyperlipidemia is crucial in the prevention of CHD. Primary, secondary, and angiographic trials have demonstrated the beneficial effects of lipid-lowering drugs, especially statins, in the reduction of CHD associated mortality and morbidity. These benefits have been observed irrespective of the age group, cholesterol levels, CHD risk factors, and in the presence or absence of prior CHD.

Given the beneficial effects of statin therapy in the prevention of CHD, compliance with these drugs and the effective monitoring of drug response are important in the management of hyperlipidemia. The Adult Treatment Panel (ATP) calls for monitoring of lipid levels and monitoring of adverse events for patients initiated on statin therapy. Frequent monitoring of drug response, as well as, monitoring of side effects by conducting liver function tests (LFTs) is crucial for the success of statin drug therapy. The purpose of the study was to evaluate drug utilization patterns, medication adherence, and lipid and safety monitoring of patients on statin drug therapy in the Texas Medicaid

[438] Farnier M, Davignon J. Current and future treatment of hyperlipidemia: the role of statins. *American Journal of Cardiology.* 1998;82(4B):3J-10J.

system. This chapter presents a summary and discussion of the study results. Limitations of the study are also discussed. Finally, the chapter concludes with the suggestions for future research, overall study conclusion and implications of the study to Texas Medicaid.

The results are discussed in six sections: (1) demographic characteristics; (2) clinical conditions; (3) use of statins and other lipid lowering drugs; (4) specialty of physician prescribing statin at index date; (5) compliance with statin therapy; (6) lipid and liver function monitoring.

DEMOGRAPHIC CHARACTERISTICS

The majority of patients in this study were females (65.2%). Texas Medicaid is comprised mainly of women (56%) and non-disabled children (59%).[439] The present study included only patients between 21-64 years; the mean age of patients in the study at index date was 49.7 years. The reason patients 65 or older were not a part of the study was because the medical claims for individuals above 65 years of age may be incomplete due to dual eligibility in Medicaid and Medicare programs. The age of the subjects is slightly lower than the average age of statin users in other studies conducted in primary care settings. In those studies, the mean age of new statin users was 58.5 years,[440,441,442]

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[439] Texas Health and Human Services Commission. Clients and Benefits. *Texas Medicaid in Perspective*. Austin; 2004:4-1-4-24.
[440] Catalan V, LeLorier J. Predictors of long-term persistence on statins in a subsidized clinical population. *Value in Health.* 2000;3(6):417-426.
[441] Harley CR, Setareh WA, McDonough KL, et al. Cholesterol management in a population of managed care enrollees. *Journal of Clinical Outcomes Management.* 2003;10(3):147-154.

except in studies that were conducted in the Medicaid population[443,444] and those conducted in nursing home settings,[445] which included patients 65 years and older.

A total of 42.7 percent of the patients were non-Hispanic whites, followed by Hispanics (N = 2,304; 32.7%) and non-Hispanic blacks (N = 1,585; 22.5%). A greater percentage of non-Hispanic whites in this study suffered from hyperlipidemia and were on statin drugs. This finding is not surprising; based on the statistics from the state of Texas, there is a higher prevalence of hyperlipidemia among whites (35.2%) than other ethnic minorities such as African Americans (29.2%) and Hispanics (24.5%).[446] The findings are also consistent with those obtained from a national sample where, based on the ATP II guidelines, a greater percentage of whites (29.5%) qualified for dietary and drug therapy, compared to non-Hispanic blacks (24.7%), and Mexican-Americans

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[442] White J, Chang E, Leslie S, et al. Patient adherence with HMG reductase inhibitor therapy among users of two types of prescription services. *Journal of Managed Care Pharmacy.* 2002;8(3):186-191.

[443] Avorn J, Monette J, Lacour A, et al. Persistence of the use of lipid lowering medications: A cross national study. *Journal of the American Medical Association.* 1998;279(18):1458-1452.

[444] Benner J, Glynn R, Mogun H, et al. Long-term persistence in use of statin therapy in elderly patients. *Journal of the American Medical Association.* 2002;288(4):455-461.

[445] Eaton C, Lapane K, Murphy J, et al. Effect of statin (HMG-CoA reductase inhibitor) use on 1-year mortality and hospitalization rates in older patients with cardiovascular disease living in nursing homes. *Journal of American Geriatric Society.* 2002;50(8):1389-1395.

[446] Cardiovascular Health and Wellness Program. Cardiovascular Disease (CVD) in Texas: A surveillance report and program strategy 2003. *Bureau of Chronic Disease and Tobacco Prevention, Texas Department of Health*. Available at: http://www.tdh.state.tx.us/wellness/cvd/cvdsurv2003.pdf. Accessed November 17, 2003.

(18.2%) [447] This study can only be generalized to the Texas Medicaid population and lacks generalizability to other populations.

CLINICAL CONDITIONS

The majority of the statin users (75.0%) were classified as primary prevention patients, i.e., they did not have a diagnosis of CHD within a year prior to the start of therapy. This shows that statins were primarily used for the prevention of CHD. Over half of the patients had a hypertension diagnosis at or prior to index date, and a little less than half had a diagnosis for diabetes at or a year prior to index date. The majority of the diabetics (96.5%) were type 2 diabetics. Over half (51.7%) of the primary prevention patients in the present study were type 2 diabetics. Other risk factors such as age and gender were also assessed. According to the ATP guidelines, males below 45 years of age, and females over 55 years have an increased risk of CHD.[448] In this study, 45.9 percent of the patients were males greater than 45 years and females over 55 years. Overall, the mean number of CHD risk factors in the study population was 1.5 (S.D. = 0.9).

[447] Hoerger TJ, Bala MV, Bray JW, et al. Treatment patterns and distribution of low-density lipoprotein cholesterol levels in treatment-eligible United States adults. *American Journal of Cardiology.* 1998;82(1):61-65.

[448] Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults. Summary of the Second Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *Journal of the American Medical Association.* 1993;269(23):3015-3023.

The high prevalence of statin use among patients with risk factors such as diabetes and hypertension follows the recommendations by the ATP guidelines to aggressively treat hyperlipidemia among patients with these risk factors. As per the ATP III guidelines, diabetes confers an absolute, 10-year risk for developing major coronary events equal to that of a person with CHD; thus, there is a need to aggressively treat hyperlipidemia among diabetics. The majority of the diabetics in the present study were type 2 diabetics; this finding is consistent with the national statistics, where according to the National Diabetes Database Clearinghouse, around 90-95 percent of diabetics have type 2 diabetes.[449] The American College of Physicians guidelines recommend the treatment of hyperlipidemia among diabetics, particularly type 2 diabetics.[450] The higher prevalence of diabetes among statin users in this study population could be attributed to increased awareness for treating this important risk factor for CHD and the publishing of primary[451,452] and secondary prevention[453,454] trials showing the beneficial effects of statins.

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[449] National Diabetes Information Clearinghouse. Diabetes Overview. Available at: http://diabetes.niddk.nih.gov/dm/pubs/overview/index.htm. Accessed December 1, 2004.
[450] Snow V, Aronson MD, Hornbake ER, et al. Lipid control in the management of type 2 diabetes mellitus: A clinical practice guideline from the American College of Physicians. *Annals of Internal Medicine.* 2004;140(8):644-649.
[451] Kjekshus J, Berg K, Pedersen TR, et al. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study (4S). *The Lancet.* 1994;344(8934):1383-1389.
[452] Shepherd J, Blauw G, Murphy J, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): A randomised controlled trial. *The Lancet.* 2002;360(9346):1623-1630.
[453] Pedersen TR, Olsson AG, Færgeman O, et al. Lipoprotein Changes and Reduction in the Incidence of Major Coronary Heart Disease Events in the Scandinavian Simvastatin Survival Study (4S). *Circulation.* 1998;97(15):1453-1460.

USE OF STATINS AND OTHER-LIPID LOWERING DRUGS

The most commonly prescribed statins, based on the total number of prescription claims for the two-year follow-up period were Lipitor® (57.1%), Zocor® (23.2%) and Pravachol® (14.2%). Overall, only 11.6 percent of the total patients were taking other lipid lowering drugs (non-statin drugs) such as fibrates (8.3%), bile acid sequestrants (1.6%), and nicotinic acid derivatives (1.5%). This finding is not surprising, since statins are the most widely prescribed lipid lowering therapy and are recommended as the first line of drug therapy under the ATP guidelines. The use of other lipid lowering drugs has decreased since the introduction of statins. Studies have shown similar results, where majority of the patients were initiated on statin therapy for the treatment of hyperlipidemia, followed by fibrates and other lipid lowering therapy.[455,456] In the present study, a majority (78.7%) of the statin users were initiated on a statin drug at the recommended starting dose. Based on the package inserts, the recommended starting doses for the statins were as follows: Lipitor® 10 or 20 mg once daily;[457] Zocor® 20 or

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[454] Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *New England Journal of Medicine.* 1996;335(14):1001-1009.
[455] Sueta C, Chowdhury M, Boccuzzi S, et al. Analysis of the degree of undertreatment of hyperlipidemia and congestive heart failure secondary to coronary artery disease. *American Journal of Cardiology.* 1999;83(9):1303-1307.
[456] Yang Y, Kao S, Chan A. A retrospective drug utilization evaluation of antihyperlipidaemic agents in a medical centre in Taiwan. *Journal of Clinical Pharmacy & Therapeutics.* 1997;22(4):291-299.
[457] Lipitor package insert. Morris Plains, NJ: Parke-Davis; April 2003.

40 mg once daily;[458] Pravachol® 40 mg once daily;[459] Lescol® 40 mg once daily;[460] and Mevacor® 20 mg once daily.[461] There were no practical differences in the dose prescribed at the index date of statin drugs between CHD and non-CHD patients. Similar findings were reported by Sueta et al., where most patients were on the recommended starting dose and 65 percent of patients with CHD were on the recommended starting dose.[462] Although calculating a mean dose across drug products has its limitations, in the present study, the mean daily dose on which the patients were started on was 19.2 mg, which is consistent with that reported in the study by Catalan et al.,[463] where the mean initial statin dose was 18 mg.

In the present study, only 31.6 percent (N = 2,352) of the patients received a prescription for an increase in statin dose following the start of therapy. Gaw et al. stated that in primary care settings, physicians often fail to achieve the recommended LDL goals for their patients due to a number of factors including lack of adequate effectiveness of lipid-lowering drugs in reducing the LDL levels in frequently used

[458] Zocor package insert. West Point, PA: Merck & Co.; April 2003.
[459] Pravachol package insert. Princeton, NJ: Bristol-Myer Squibb Company. April 2003.
[460] Lescol package insert. East Hanover, NJ: Novartis Pharmaceuticals; April 2003.
[461] Mevacor package insert. West Point, PA: Merck & Co.; April 2003.
[462] Sueta C, Chowdhury M, Boccuzzi S, et al. Analysis of the degree of undertreatment of hyperlipidemia and congestive heart failure secondary to coronary artery disease. *American Journal of Cardiology.* 1999;83(9):1303-1307.
[463] Catalan V, LeLorier J. Predictors of long-term persistence on statins in a subsidized clinical population. *Value in Health.* 2000;3(6):417-426.

doses.[464] Failure to achieve lipid goals are attributed to a large extent to inadequate doses of lipid-lowering agents. As found in this study, most patients who began statin treatment remained at the initial dose. As per the NCEP guidelines, the decision to initiate lipid lowering therapy is based on the LDL cholesterol levels, the number of risk factors, and presence or absence of CHD. In the Texas Medicaid database, the information on LDL levels as well as risk factors such as smoking status, family history of CHD were absent; thus, it was not possible to evaluate if statin therapy was initiated appropriately based on the guidelines.

SPECIALTY OF PHYSICIAN PRESCRIBING THE STATIN AT INDEX DATE

Family practice/general practice physicians (44.6%) and internal medicine physicians (32.3%) wrote a majority of the prescriptions at the index date, whereas, only 7.9 percent of the statin prescriptions were written by a cardiologist. It is important to note that the number of patients treated by cardiologists was lower than that seen in managed care organizations or primary care settings, where 28 percent and nine percent of the index prescriptions were written by cardiologists, respectively.[465,466] One possible reason for this difference is the lack of access to specialists due to the indigent nature of the Medicaid population.

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[464] Gaw A. A new reality: achieving cholesterol-lowering goals in clinical practice. *Atherosclerosis Supplements.* 2002;2(4):5-8.
[465] Harley CR, Setareh WA, McDonough KL, et al. Cholesterol management in a population of managed care enrollees. *Journal of Clinical Outcomes Management.* 2003;10(3):147-154.
[466] Maviglia SM, Teich JM, Fiskio J, et al. Using an electronic medical record to identify opportunities to improve compliance with cholesterol guidelines. *Journal of General Internal Medicine.* 2001;16(8):531-537.

COMPLIANCE WITH STATIN THERAPY

Compliance with statin therapy was estimated using the medication possession ratio (MPR) and number of days of persistence with the therapy. Persistence was assessed as the length of time until statin therapy discontinuation. A gap of 60 days after exhausting the last medication supply was used as defining discontinuation. A sensitivity analysis was also conducted using a gap of 45 days. The mean MPR was 0.7 and over half of the patients had an MPR of less than 0.80. The mean MPR in this study was slightly lower than that seen in other studies; however, it should be noted that these studies were not conducted in the Medicaid population. The literature lacks information about adherence to statin therapy for the Medicaid population under 65 years of age. The mean MPR in the study that used pharmacy claims from a managed care organization was slightly higher (0.8) than the one observed in the present study. However, the study included only secondary prevention patients who had experienced an acute MI or atherosclerotic disease.[467] Another study that used information from an HMO showed a mean MPR of 0.8 for those filling prescription in a community pharmacy; however, the mean age of the patients in the study was 61.4 years.[468]

Using the 60 -day gap for failing to refill the prescription, the mean number of days of persistency to statin therapy was 381 days (95% CI: 374.0-389.0). Only 50 percent of the patients were persistent with their statin therapy at the end of 310 days, and

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[467] Coombs JH, Cornish L, Hiller P, et al. Compliance and refill pattern behavior with HMG-CoA reductase inhibitors after acute myocardial infarction. *Managed Care Interface.* 2002;15(1):54-58.

[468] White J, Chang E, Leslie S, et al. Patient adherence with HMG reductase inhibitor therapy among users of two types of prescription services. *Journal of Managed Care Pharmacy.* 2002;8(3):186-191.

the probability of being persistent at the end of the two-year follow-up was 0.41. The number of days of persistence for 17.8 percent of the patients was zero, implying that 17.8 percent of the patients exceeded the 60-day gap after getting their first statin prescription filled. In other words, close to one in five patients did not get their first statin prescription refilled within 60-days after the last day of therapy. There was a sharp fall in persistence in the first year of therapy, but the fall decreased gradually over time after 12 months. These results were consistent with other studies which showed a slowdown in the rate of discontinuation after the first year.[469,470]

Sensitivity analysis using a gap of 45 days showed a similar pattern of statin therapy discontinuation over time. Based on a 45-day gap of failing to refill the prescription, the mean days of persistency to statin therapy was 329 days (95% CI: 321.8-336.5). The days of persistence for 21.8 percent of the patients (N = 1,620) was zero, implying that these patients exceeded the 45-day gap for their first statin prescription refill. Only 50 percent (N = 3,720) of the patients were persistent with their statin therapy at the end of 206 days. The probability of being persistent at the end of the two year follow-up period was 0.33. The number of days of persistence for 21.8 percent of the patients was zero, implying that 21.8 percent of the patients exceeded the 45-day gap after getting their first statin prescription filled. As observed with the 60-day gap, there was a sharp fall in persistence in the first year of therapy, but the fall decreased gradually

[469] Jackevicius C, Mamdani M, Tu J. Adherence with statin therapy in elderly patients with and without acute coronary syndromes. *Journal of the American Medical Association.* 2002;288(4):462-467.
[470] Benner J, Glynn R, Mogun H, et al. Long-term persistence in use of statin therapy in elderly patients. *Journal of the American Medical Association.* 2002;288(4):455-461.

over time after 12 months. These results were consistent with other studies which showed a slowdown in the rate of discontinuation after the first year.[471,472,473] The results point to a need to find a means of improving patient adherence within the first few months of therapy since patients are more likely to stop therapy early on than later. Statins are expensive drugs and most often statin therapy is a life long therapy. If half the people are discontinuing their therapy, then the full benefit of the drug is not being achieved. Texas Medicaid is wasting its resources if the patients are discontinuing therapy and there is an increased risk of long-term costs associated with CHD.

The discontinuation rates in the present study were 52.6 percent at the end of one year, and 59.3 percent at the end of two years. Based on the study results, the discontinuation rates in the present study are higher than those observed in clinical trials (4-15%) and those observed by Andrade et al. (15%).[474] The rate was lower than those observed in studies conducted by Simons and Catalan where the discontinuation rates were 60% and 67% at the end of one year, respectively.[475,476] However, it should be noted that these studies were not conducted among the Medicaid population and included

[471] Benner J, Glynn R, Mogun H, et al. Long-term persistence in use of statin therapy in elderly patients. *Journal of the American Medical Association.* 2002;288(4):455-461.
[472] Jackevicius C, Mamdani M, Tu J. Adherence with statin therapy in elderly patients with and without acute coronary syndromes. *Journal of the American Medical Association.* 2002;288(4):462-467.
[473] Catalan V, LeLorier J. Predictors of long-term persistence on statins in a subsidized clinical population. *Value in Health.* 2000;3(6):417-426.
[474] Andrade SE, Walker AM, Gottolieb LK, et al. Discontinuation of antihyperlipidemic drugs-do rates reported in clinical trials reflect rates in primary care settings? *New England Journal of Medicine.* 1995;332(17):1125-1131.
[475] Simons L, Simons J, McManus P, et al. Discontinuation rates for use of statins are high. *British Medical Journal.* 2000;321(7268):1084-.
[476] Catalan V, LeLorier J. Predictors of long-term persistence on statins in a subsidized clinical population. *Value in Health.* 2000;3(6):417-426.

older patients. There were two studies that were conducted in the Medicaid population, but both studies included patients above the age of 65 years.[477,478] In these studies, 43 percent of the patients were persistent at the end of six months and the two-year adherence rate was 36.1 percent among secondary prevention patients, and 25.4 percent among primary prevention patients.

Texas Medicaid patients are entitled to receive at least three prescriptions per month without a charge. Thus, in the vast majority of the cases economics cannot be blamed for the poor persistence because quantities of drug therapies are usually adjusted so that a patient may be taking more than three drug products, but have them filled at different months. However, despite prescription coverage, Medicaid recipients have reported a higher rate of non-compliance due to high costs of prescription drugs.[479] Despite the fact that drug quantities are used to get around the three prescriptions per month limit, Medicaid recipients could incur out of pocket expenses for drugs which could lead to discontinuation of therapy.

The majority of the patients in the study were females and primary prevention patients. Heart disease is often viewed as a "male disease" and women may not view themselves at as high a risk as compared to men; thus, they may not perceive the importance of controlling hyperlipidemia. Since hyperlipidemia is a silent disease,

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[477] Benner J, Glynn R, Mogun H, et al. Long-term persistence in use of statin therapy in elderly patients. *Journal of the American Medical Association.* 2002;288(4):455-461.
[478] Jackevicius C, Mamdani M, Tu J. Adherence with statin therapy in elderly patients with and without acute coronary syndromes. *Journal of the American Medical Association.* 2002;288(4):462-467.
[479] Kennedy J, Coyne J, Sclar D. Drug affordability and prescription noncompliance in the United States: 1997-2002. *Clinical Therapeutics.* 2004;26(4):607-614.

primary prevention patients who have not yet experienced CHD may not understand the importance of treating high cholesterol.

Despite the claim that statins are well-tolerated, physicians view side-effects of statins to be one of the barriers to treatment.[480] The risk of statin-associated myopathy increases with the concomitant use of other drugs and in special populations such as elderly, and those with impaired metabolic processes.[481] There could be a possibility that potential drug-drug interactions could have increased the occurrence of side-effects and led to statin discontinuation in this study population. However, due to the lack of data, this cannot be confirmed. It is noteworthy to mention that in clinical trials, such as the WOSCOPS and 4S, the rates of adverse events and withdrawal from the study did not differ between the statin and the placebo group.[482,483] However, the withdrawal of statin drug cerivastatin due to increased risk of rhabdomylosis,[484] as well as the more recent safety concern on the latest statin drug rosuvastatin[485] has put forth concerns about the

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[480] Pasternak RC, Mckenney J, Brown V, et al. Understanding physician and consumer attitudes concerning cholesterol management: Results from the National Lipid Association Surveys. *American Journal of Cardiology.* 2004;94(9A):9F-157.
[481] Pasternak RC, Smith S, Bairey-Merz CN, et al. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *Journal of the American College of Cardiology.* 2002;40(3):567-572.
[482] Shepherd J, Cobbe S, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *New England Journal of Medicine.* 1995;333(20):1301-1307.
[483] Kjekshus J, Berg K, Pedersen TR, et al. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study (4S). *The Lancet.* 1994;344(8934):1383-1389.
[484] Jamal SM, Eisenberg MJ, Christopoulos S. Rhabdomyolysis associated with hydroxymethylglutaryl-coenzyme A reductase inhibitors. *American Heart Journal.* 2004;147(6):956-965.
[485] Wolfe SM. Dangers of rosuvastatin identified before and after FDA approval. *Lancet.* 2004;363(9427):2189-2190.

safety of this class of drugs. The database did not have laboratory values of the liver function tests (LFTs) to evaluate if the rate of occurrence of adverse events was associated with poor compliance.

In further analysis of adherence, a multiple regression and Cox regression analyses were employed to assess predictors of MPR and persistence, respectively. MPR was used as the dependent variable in one model while days until statin therapy discontinuation were used as the dependent variable in the other. In a previous study, the MPR was dichotomized into compliant (MPR greater than 80 percent) and non-compliant (MPR less than 80 percent) groups and logistic regression was employed. An MPR of 80 has been the threshold used in clinical trials; however, it may not be appropriate in "real-world" settings. The predictors in the model used in this study were patient's age at index date, gender, ethnicity, presence of CHD, diabetes, hypertension, atherosclerotic diseases, and total number of prescriptions other than lipid-lowering drugs during the two-year follow-up period. The multiple regression results showed that being male, non-Hispanic white and the absence of CHD, hypertension and diabetes were associated with an increase in MPR.

Cox regression analysis was employed to assess the predictors of persistence. The time until statin therapy discontinuation was used as the dependent variable in the model. The predictors of persistence were assessed using a Cox regression model with time until statin therapy discontinuation as the dependent variable. The Cox regression yielded similar results, where being male and white were associated with a lower hazard of becoming non-persistent, whereas the presence of disease conditions (except for

atherosclerotic disease) was associated with a greater hazard of becoming non-persistent to statin therapy.

Results showed that female gender was associated with decreased adherence and this result was consistent with the results obtained by Sung et al.,[486] and Andrade et al.[487] Andrade et al. attributed the higher rates of discontinuation of lipid lowering therapy among females to the occurrence of adverse events. Due to the data limitations, the rate of occurrence of adverse events associated with the use of statins could not be evaluated. Another potential reason for higher discontinuation rate among females could be the perception that CHD is a male disease and females are less susceptible to it. Thus, the management of hyperlipidemia, which is a major risk factor for the occurrence of CHD, may not be viewed that important by females as compared to males.

Age was not a significant predictor of MPR or persistence to statin therapy. This is consistent with the literature where most studies do not show an association of age[488,489,490,491] with adherence, except for one, where older age was associated with poor long-term persistence, but this study included elderly patients.[492] Consistent with other

[486] Sung JCY, Nichol MB, Venturini F, et al. Factors affecting patient compliance with antihyperlipidemic medication in an HMO population. *American Journal of Managed Care.* 1998;4(10):1421-1430.
[487] Andrade SE, Walker AM, Gottolieb LK, et al. Discontinuation of antihyperlipidemic drugs-do rates reported in clinical trials reflect rates in primary care settings? *New England Journal of Medicine.* 1995;332(17):1125-1131.
[488] Catalan V, LeLorier J. Predictors of long-term persistence on statins in a subsidized clinical population. *Value in Health.* 2000;3(6):417-426.
[489] Andrade SE, Walker AM, Gottolieb LK, et al. Discontinuation of antihyperlipidemic drugs-do rates reported in clinical trials reflect rates in primary care settings? *New England Journal of Medicine.* 1995;332(17):1125-1131.

studies in the literature[493,494,495,496],there exists an ethnic disparity in adherence to statin therapy, with whites being more adherent than other ethnic groups. Using multiple regression analysis, a negative relationship was found between MPR and non-Hispanic blacks (Beta = -0.127, $p < 0.001$), and MPR and Hispanics (Beta = -0.130, $p < 0.001$). These ethnic groups had a lower MPR as compared to non-Hispanic whites, controlling for age, gender, disease conditions, and total number of prescriptions.

Disease conditions such as CHD, diabetes, hypertension, and the presence of atherosclerotic diseases were assessed prior to or at the index date and during the follow-up period. These variables were included in the model to assess their relationship with MPR and persistence. Presence of diabetes during follow-up, hypertension both prior and during follow-up, and presence of CHD both prior to and after the start of therapy had a negative relationship with MPR. The presence of diabetes prior to index date, presence of CHD, hypertension both prior to and during the follow-up period were

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[490] Avorn J, Monette J, Lacour A, et al. Persistence of the use of lipid lowering medications: A cross national study. *Journal of the American Medical Association.* 1998;279(18):1458-1452.

[491] Sung JCY, Nichol MB, Venturini F, et al. Factors affecting patient compliance with antihyperlipidemic medication in an HMO population. *American Journal of Managed Care.* 1998;4(10):1421-1430.

[492] Benner J, Glynn R, Mogun H, et al. Long-term persistence in use of statin therapy in elderly patients. *Journal of the American Medical Association.* 2002;288(4):455-461.

[493] Ellis JJ, Erickson SR, Stevenson JG, et al. Suboptimal statin adherence and discontinuation in primary and secondary prevention populations. *Journal of General Internal Medicine.* 2004;19(6):638-645.

[494] Benner J, Glynn R, Mogun H, et al. Long-term persistence in use of statin therapy in elderly patients. *Journal of the American Medical Association.* 2002;288(4):455-461.

[495] Kaplan RC, Bhalodkar NC, Brown EJ, et al. Race, ethnicity and sociocultural characteristics predict noncompliance with lipid-lowering medications. *Preventive Medicine.* 2004;39:1249-1255.

[496] Charles H, Good CB, Hanusa B, et al. Racial differences in adherence to cardiac medications. *Journal of National Medical Association.* 2003;95(1):17-27.

significant predictors of poor persistence to statin therapy. These results are contrary to what is observed in the literature, where in a majority of the studies, except in one, [497] the presence of CHD was associated with increased compliance with lipid lowering therapy.[498,499,500,501,502] Similarly, the presence of other disease conditions, such as diabetes, hypertension and atherosclerotic diseases that impose a risk for CHD were associated with improved compliance. However, some of these studies have included elderly patients.[503,504,505] The presence of CHD had no effect on patient adherence in one study; however, it should be noted that this study classified diabetics as secondary

[497] Maviglia SM, Teich JM, Fiskio J, et al. Using an electronic medical record to identify opportunities to improve compliance with cholesterol guidelines. *Journal of General Internal Medicine.* 2001;16(8):531-537.
[498] Avorn J, Monette J, Lacour A, et al. Persistence of the use of lipid lowering medications: A cross national study. *Journal of the American Medical Association.* 1998;279(18):1458-1452.
[499] Benner J, Glynn R, Mogun H, et al. Long-term persistence in use of statin therapy in elderly patients. *Journal of the American Medical Association.* 2002;288(4):455-461.
[500] Catalan V, LeLorier J. Predictors of long-term persistence on statins in a subsidized clinical population. *Value in Health.* 2000;3(6):417-426.
[501] Jackevicius C, Mamdani M, Tu J. Adherence with statin therapy in elderly patients with and without acute coronary syndromes. *Journal of the American Medical Association.* 2002;288(4):462-467.
[502] Ellis JJ, Erickson SR, Stevenson JG, et al. Suboptimal statin adherence and discontinuation in primary and secondary prevention populations. *Journal of General Internal Medicine.* 2004;19(6):638-645.
[503] Benner J, Glynn R, Mogun H, et al. Long-term persistence in use of statin therapy in elderly patients. *Journal of the American Medical Association.* 2002;288(4):455-461.
[504] Avorn J, Monette J, Lacour A, et al. Persistence of the use of lipid lowering medications: A cross national study. *Journal of the American Medical Association.* 1998;279(18):1458-1452.
[505] Jackevicius C, Mamdani M, Tu J. Adherence with statin therapy in elderly patients with and without acute coronary syndromes. *Journal of the American Medical Association.* 2002;288(4):462-467.

prevention patients as well, thus the results might not be comparable to the current study.[506]

Results of this study show that compliance with statin therapy was low and the presence of CHD risk factors did not improve compliance. In other words, one would think that having a risk factor would be positively related to drug compliance, but this was not found in this study. One possible reason is that having a risk factor is related to poor maintenance of one's health and thus, it is not a surprise to observe an inverse relationship between risk factors and MPR and persistence. This calls for greater intervention by healthcare practitioners to counsel patients about the importance of lipid management, especially for patients with risk factors, since they have an increased risk of experiencing coronary events.

One study has noted that patients' perceptions of increased time spent by physicians in discussing cholesterol management and related cardiovascular issues had a positive correlation with increased compliance.[507] However, patients' perceptions about the role of cholesterol in the development of cardiovascular diseases (CVD) and their own personal views about their risk of developing a CVD event did not influence adherence to lipid lowering therapy.[508] This may be the one of the reasons for the lack of

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[506] Ellis JJ, Erickson SR, Stevenson JG, et al. Suboptimal statin adherence and discontinuation in primary and secondary prevention populations. *Journal of General Internal Medicine.* 2004;19(6):638-645.
[507] Kiortsis D, Giral P, Bruckert E, et al. Factors associated with low compliance with lipid-lowering drugs in hyperlipidemic patients. *Journal of Clinical Pharmacy & Therapeutics.* 2000;25(6):445-451.
[508] Kiortsis D, Giral P, Bruckert E, et al. Factors associated with low compliance with lipid-lowering drugs in hyperlipidemic patients. *Journal of Clinical Pharmacy & Therapeutics.* 2000;25(6):445-451.

adherence to statin therapy among patients in the present study. This reemphasizes the importance of counseling by healthcare practitioners on management of hyperlipidemia and reenforcing the importance of adherence to lipid lowering therapy in preventing CHD, as well as promoting the understanding of the association between hyperlipidemia and the increased risk of CHD. Based on the literature, there appears to be scope for improvement in lipid management as only few physicians think that they are doing a good job in educating patients about the risks of high cholesterol and also there is a general lack of knowledge about the link between high cholesterol and CHD.[509]

Based on a study that assessed patients' perceptions of statin therapy for the treatment of hyperlipidemia,[510] patients who were compliant with their statin therapy mentioned that their health care providers explained the importance and benefits of statin therapy and in some instances, the providers mentioned the consequences of hyperlipidemia. Among patients who had discontinued their medications, the main issue was the absence of symptoms associated with raised cholesterol and their perception of being "healthy." The above provides the opportunity for health care providers to intervene and promote adherence to statin therapy by explaining the consequences of the lack of adherence.

The total number of prescriptions that the patients were taking other than statins was evaluated as one of the predictors to MPR and persistence. The mean number of

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[509] Pasternak RC, Mckenney J, Brown V, et al. Understanding physician and consumer attitudes concerning cholesterol management: Results from the National Lipid Association Surveys. *American Journal of Cardiology.* 2004;94(9A):9F-157.
[510] Tolmie EP, Lindsay GM, Kerr SM, et al. Patients' perspectives on statin therapy for treatment of hypercholesterolaemia: a qualitative study. *European Journal of Cardiovascular Nursing.* 2003;2(2):141-149.

total other prescriptions in the current study during the two-year follow-up period was 15.70 (S.D. = 10.2). This variable was not a significant predictor of adherence while controlling for demographics and disease conditions. Studies have assessed the influence of number of medications dispensed either prior to the start of lipid lowering therapy or during the study period. Some studies have shown a negative relationship between increased number of prescriptions dispensed and adherence,[511,512,513,514] whereas other studies have shown no relationship.[515,516]

LIPID AND LIVER FUNCTION MONITORING

The ATP II guidelines recommend lipid monitoring prior to initiating drug therapy as well as follow-up measurements. Based on the guidelines, it is important to have a minimum of two lipoprotein measurements during one to two months of diet therapy prior to initiating the drug therapy. After starting drug therapy, the first

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[511] Benner J, Glynn R, Mogun H, et al. Long-term persistence in use of statin therapy in elderly patients. *Journal of the American Medical Association.* 2002;288(4):455-461.
[512] Coombs JH, Cornish L, Hiller P, et al. Compliance and refill pattern behavior with HMG-CoA reductase inhibitors after acute myocardial infarction. *Managed Care Interface.* 2002;15(1):54-58.
[513] Kiortsis D, Giral P, Bruckert E, et al. Factors associated with low compliance with lipid-lowering drugs in hyperlipidemic patients. *Journal of Clinical Pharmacy & Therapeutics.* 2000;25(6):445-451.
[514] Jackevicius C, Mamdani M, Tu J. Adherence with statin therapy in elderly patients with and without acute coronary syndromes. *Journal of the American Medical Association.* 2002;288(4):462-467.
[515] Coombs JH, Cornish L, Hiller P, et al. Compliance and refill pattern behavior with HMG-CoA reductase inhibitors after acute myocardial infarction. *Managed Care Interface.* 2002;15(1):54-58.
[516] Abhughosh SM, Kogut SJ, Andrade SE, et al. Persistence with lipid lowering therapy: Influence of the type of lipid-lowering agent and drug benefit plan option in elderly patients. *Journal of Managed Care Pharmacy.* 2004;10(5):404-411.

lipoprotein measurement is recommended at six to eight weeks. Once the target LDL levels are reached, patients should be monitored every eight to twelve week intervals through 52 weeks. After a year of therapy, once the LDL levels are attained, monitoring of lipids and adverse effects should be conducted at four- to six-month intervals. Monitoring for toxicity should be carried out at the same time as lipid and lipoprotein measurements.[517] In addition, the ATP III guidelines recommend lipid monitoring within six to eight weeks following a change in drug regimen.[518] Based on the criteria set in this study, monitoring for LDL levels were assessed within three months prior to the start of therapy, three months after the start of therapy and within six months thereafter. Similarly, presence of liver function tests (LFTs) was assessed during the same time intervals.

Within three months PRIOR to the start of therapy, less than half (42.5%) of the patients had their LDL levels monitored. A majority of the patients (N = 6,282; 84.4%) DID NOT have a follow-up lipid test within three months since the start of therapy; in other words, only 15.6 percent had a lipid test within three months since the start of therapy. Of those patients who had their lipid levels monitored within three months since the start of therapy (N = 1,158), only 67 patients (5.8%) had lipid monitoring within six

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[517] *Second report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II).* Bethesda (MD): U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Heart, Lung and Blood Institute; 1993. NIH Publication No: 93-3095.
[518] Grundy SM, Becker DM, Clark L, et al. Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *Journal of the American Medical Association.* 2001;285(19):2486-2497.

months thereafter. Thus, out of the total number of patients (N = 7,440), only 0.9 percent of the patients (N = 67) had their LDL levels monitored as per the criteria.

It is disturbing to find that over half of the patients were started on statin therapy without having their LDL levels tested. It could be due to the fact that majority of the patients had risk factors such as diabetes and hypertension and these risk factors call for aggressive management of cholesterol. Physicians might start the patient on statins based on the presence of the CHD risk factors. Nevertheless, lack of testing the LDL levels prior to start of therapy cannot be justified by the presence of risk factors; rather it denotes either poor patient care on the part of the physician or lack of patient compliance with lipid tests. Prior to the index date only 53.1 percent (N = 3,954) had a diagnosis for hyperlipidemia. Of those without a diagnosis for hyperlipidemia prior to index date 67.7 percent (N = 2,361) presented with a diagnosis in the follow-up period. This could be due to the fact that hyperlipidemia may not always be coded in the medical claims file. Under-reporting of hyperlipidemia was also observed in a study by Lewis et al., where of only 43 percent of the patients had a diagnosis for hyperlipidemia.[519] Also, missing data could be a contributing factor to the low occurrence of LDL monitoring tests and LFTs.

Within a year following the start of therapy, only 49.9 percent of the patients had their LDL levels measured. This is low compared to a managed care organization, where 60 percent of statin users had a claim for cholesterol monitoring in the first year of

[519] Lewis BE, KL M. Dyslipidemia treatment among patients with coronary artery disease in a managed care organization. *American Journal of Health System Pharmacy.* 2004;61:1032-1038.

follow-up.[520] Based on national Medicaid rates, in the year 2000, only 43.8 percent of patients with CHD were screened for cholesterol.[521] In the present study LDL levels were monitored in 62.9% and 56.7% of the diabetics (based on diagnosis at or year prior to index date) a year prior to and after the start of therapy. This is higher than that observed in the Texas Medicaid managed care program, where less than half (34.4%) of the diabetics had a lipid panel measured in a year of follow-up.[522] Considering the high cost of the statin drugs, it is disturbing to observe that less than half of the patients had their lipid levels tested prior to initiating statin therapy. It must be mentioned that the literature lacks information on lipid and liver function tests monitoring among Medicaid patients. These results show that adherence to the ATP guidelines is low when treating Texas Medicaid patients. It should be noted that these tests may have been ordered by physicians, but patients did not go ahead and get their lipid levels monitored. This can be compared by the findings by O'Donnell et al., where despite being advised by pharmacists to get their lipid levels tested within six months after discharge from a lipid

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[520] Harley CR, Setareh WA, McDonough KL, et al. Cholesterol management in a population of managed care enrollees. *Journal of Clinical Outcomes Management.* 2003;10(3):147-154.

[521] American Heart Association. Heart Disease and Stroke Statistics - 2004 Update. *American Heart Association*. Available at: http://www.americanheart.org/presenter.jhtml?identifier=1928. Accessed January 15, 2004.

[522] Texas Medicaid Managed Care 2001: Star+Plus Diabetes Focused Study. Available at: http://www.hhsc.state.tx.us/medicaid/mc/about/reports/2001annrpts/StarPlus_Diabetes_SFY2001_Tech.pdf. Accessed December 15, 2004.

clinic, only about half of them got themselves tested.[523] However, due to the data limitations, this could not be evaluated. In addition, this study found that the monitoring of LDL levels after changes in therapy was suboptimal. Following a change in therapy, only 15.5 (N = 335) and 14.1 percent (N = 178) of the patients who had a change in statin type or dose, respectively, had their LDL monitored.

Only 14.7 percent (N = 3,163) of the total patients had a liver function test (LFT) within three months PRIOR to the start of therapy, and only 9.7 percent (N = 724) of the patients had a LFT within three months since the start of therapy. Of those patients who had their liver function monitored within three months since the start of therapy (N = 724), only 35 patients (4.8%) had LFTs within six months thereafter. A greater number of patients had LFTs within a year as compared to three months since the start of therapy (31.6% vs. 9.7%). One possible explanation could be that physicians are ignoring the guidelines and might be ordering tests only if the patient complains of muscle pain or weakness. The lack of LFTs could also be explained by the fact that the risk of occurrence of statin-associated myopathy is greater at higher doses, and the majority of the patients in the study were on low (5mg, 10mg or 20mg) doses. Due to this, physicians might not be viewing monitoring for side-effects to be cost-effective. There have been no known studies that have evaluated the rate of occurrence of LFTs in patients on statins. However, one study looked at safety monitoring among patients on

[523] O'Donnell DC, Chen NT, Piziak V. Goals attainment and maintenance of serum cholesterol level in a pharmacist-coordinated lipid clinic. *American Journal of Health System Pharmacy*. 2001;58:325-330.

lipid lowering drugs in a pharmacist run lipid management clinic, 95 percent of the patients received safety monitoring at least once a year.[524]

There are no known studies in the literature that have assessed the predictors of lipid tests in the Medicaid population or in the general population. The factors significantly associated with an increased likelihood of having a lipid test at baseline, included female gender, younger age, being white, absence of CHD, presence of diabetes and hypertension. Being non-Hispanic white was associated with an increased likelihood of a lipid test compared to other ethnic groups, except for Hispanics who had an increased likelihood of lipid tests compared to whites. In addition, having a diagnosis for CHD was associated with a decreased likelihood of having a lipid test. This is an unexpected finding since it would be desired that monitoring of lipid levels would be higher for those patients who had a prior history of CHD. Similarly, Hispanics having a greater likelihood of being tested compared to whites was an unexpected finding since it has been reported that ethnic minorities have a lower rate of cholesterol screening.[525]

When the predictors of lipid testing after the start of therapy were assessed, non-Hispanic whites had a greater likelihood of having a lipid test compared to non-Hispanic Blacks. Contrary to the results obtained for baseline lipid testing, prior CHD as well as prior lipid monitoring were significantly associated with increased likelihood of LDL

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[524] O'Donnell DC, Chen NT, Piziak V. Goals attainment and maintenance of serum cholesterol level in a pharmacist-coordinated lipid clinic. *American Journal of Health System Pharmacy*. 2001;58:325-330.

[525] Nelson K, Norris K, Mangione CM. Disparities in the diagnosis and pharmacologic treatment of high serum cholesterol by race and ethnicity: data from the Third National Health and Nutrition Examination Survey. *Archives of Internal Medicine.* 2002;162(8):929-935.

monitoring following the start of statin therapy. Prior lipid testing also was a significant predictor of LDL monitoring following a change in therapy or an increase in statin dose. Since CHD patients are considered as high risk patients, monitoring of lipid levels was greater compared to non-CHD patients. Lipid testing prior to the start of therapy should be promoted since this is a positive predictor of future lipid monitoring. Suboptimal LDL monitoring may indicate a lack of patient compliance since the physicians could have ordered these tests but the patients might not be completing the tests.

The factors associated with an increased likelihood of LFTs prior to the start of therapy were younger age, presence of diabetes and hypertension. However, older age, being non-Hispanic black and presence of hypertension were associated with an increased likelihood of LFTs after the start of therapy. Patients treated by a cardiologist at the index date and those having prior LFTs had an increased likelihood of having a test following an increase in statin dose. The lower occurrence of LFTs prior to the start of therapy could be due to the fact that even though the current guidelines recommend LFTs prior to the start of therapy, there is a lack of agreement among experts regarding the need to do so. Increased likelihood of LFTs among older patients after the start of therapy could be due to the increase in the chance of occurrence of side effects with increasing age.[526]

[526] Pasternak RC, Smith S, Bairey-Merz CN, et al. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *Journal of the American College of Cardiology.* 2002;40(3):567-572.

STUDY LIMITATIONS

There are a number of study limitations which need to be addressed. The first set of limitations concerns the use of the Texas Medicaid database. Claims data may be subject to coding errors, errors in data entry and missing data. Furthermore, the data lacked information on the results of the lipid and liver function tests. Since only Texas Medicaid patients between the ages of 21 to 62 years were included in the study, the results cannot be generalized to non-Medicaid and younger or older Medicaid patients. Medicaid patients older than 21 years and not residing in a long-term care facility have a three prescription drug limit per month. Thus, patients' lack of adherence to their statin medication may be due to choices faced by patients who have more than three prescriptions per month. This could have a potential threat on the MPR and persistence. However, it must be noted that for many Medicaid patients who need more than three prescriptions per month, adjustments maybe made in quantities of drugs dispensed so a patient can be taking more than three prescription drugs. Also, if the patient bought statin drugs out-of-pocket, then no medical claim is available. Free drug samples given to the patient could also affect the adherence measures, however, this information could not be captured in the data. Furthermore, since the data lacked information on the results of LFTs, the discontinuation of statins due to abnormal LFTs could not be evaluated. Appropriate or inappropriate use of statins as per the guidelines could not be evaluated due to lack of lipid levels and information on all the risk factors.

Overall, the data were complete except for information on physician demographics and specialty as well as patient's ethnicity where there were some

missing values. Thus, results related to these variables need to be interpreted with caution. One major limitation of the study is the lack of information on other risk factors such as obesity, smoking status and family history of premature CHD. All of this information would have permitted the categorizing of patients into different risk categories as per the ATP guidelines. The presence of LDL levels would have helped in understanding the impact of adherence on the lowering of lipid levels. The lack of monitoring of lipid and LFTs could not be wholly attributed to physicians' lack of adherence to the guidelines, since the physician could have ordered the test but the patient may not have completed the test and the data did not capture this information. Due to multiple statistical tests there could be a possibility of inflated type I errors.

FUTURE RESEARCH

The current research has generated a number of questions which need to be addressed in future studies. Since this study has shown that physicians' adherence to lipid and safety monitoring guidelines is low, further research is needed to understand if indeed the physicians are not ordering the tests or the patients are not getting the tests completed and the reasons for such behavior. Perhaps a survey of physicians or an interview could be conducted to obtain information regarding their awareness of cholesterol guidelines, their perception of the importance of the guidelines, and barriers to adherence to the guidelines. It would be useful to compare physicians' orders with laboratory data. This will indicate who is at fault, the physician not ordering the tests or the patient not completing the test. A review of patient records will be required

and most likely would be an expensive study. Moreover, if physicians are ordering the tests, then it will be useful to understand the barriers that the patient faces that prohibit them from getting their lipid levels tested.

In regard to the issue of patient non-adherence to statin therapy, it would be useful to understand if the discontinuation of statins was associated with the occurrence of adverse events or increased awareness of the possible side effects of statin therapy. Medical consequences of non-adherence can also be assessed to observe if lack of adherence to statin therapy was associated with increased cardiovascular-related hospitalizations and procedures. Moreover, the rate of occurrence of statin-associated myopathy increases with the concomitant use of certain drugs. It would be interesting to evaluate if LFTs are being conducted among those patients on concomitant drugs. The rate of hospitalization due to the occurrence of statin-associated adverse events could be determined using the medical claims data. Assessing the side-effects would present a better understanding if indeed the discontinuation of therapy was due to the occurrence of statin-associated myopathy. In the present study, only the first change in dose or type of statin drug was assessed; a future study could look at subsequent changes to therapy and monitoring for LDL and side effects.

As an attempt to control the costs, Texas Medicaid implemented the prior authorization program and a preferred drug list was implemented starting March 2004. Preferred drugs do not require prior authorization while non-preferred drugs require authorization prior to dispensing. Statins such as Lipitor® was listed as a non-preferred drug. A majority of the study patients were on the statin drug Lipitor®. It would be

useful to understand if the patients on Lipitor® were switched to other drugs that were on the preferred list and also study the economic and medical consequences of such a switch.

STUDY IMPLICATIONS AND CONCLUSION

Despite the limitations, the present study presents a view of the management of hyperlipidemia among Texas Medicaid patients. The study shows the lack of adherence to statin drugs and lack of monitoring of the response to the drugs, as well as associated adverse events, both of which are probably costing Texas Medicaid program valuable dollars in the long run. Texas Medicaid should take steps to educate the physicians to be proactive in promoting patient compliance with statins, perhaps by handing out flyers and reminders to patients, to inform them about the importance for treating the condition. Moreover, efforts should also be made to educate physicians about the cholesterol guidelines as well as the importance of regular monitoring of lipid levels and adverse effects of statins.

Steps should be taken to promote the participation of health care practitioners such as pharmacists and nurses to educate patients about cholesterol management. Lipid management programs run by pharmacists could be cost-effective and efficient in promoting cholesterol management and patient adherence to lipid-lowering drugs. Similarly, nurses' intervention in educating patients on the importance of cholesterol management and its association with CHD could be very valuable. Steps also need to be taken to pass out flyers to patients to increase their awareness of the association

of high cholesterol and the occurrence of CHD. Medicaid needs to address the gender gap and ethnic disparity with respect to adherence to statins. Promoting the management of high cholesterol in primary prevention patients could save the Medicaid system long-term costs of CHD-related hospitalizations and procedures.

The primary purpose of this study was to evaluate adherence to statin therapy and monitoring of lipid and adverse events among Medicaid patients on statin therapy. The results show that adherence to statin is suboptimal. There is lack of monitoring of lipid levels and adverse events among patients on statins. The combination of the lack of adherence and inadequate monitoring of lipid levels could result in failure of the NCEP goals. Long-term costs associated with CHD could be reduced by promoting patient adherence to therapy as well as increased monitoring of lipids and adverse events.

APPENDIX A

COX PROPORTIONALITY HAZARD ASSUMPTION

Persistence Function for Categories of:

Gender

Ethnicity

Disease Conditions

Figure A.1: Persistence Function for Gender Categories

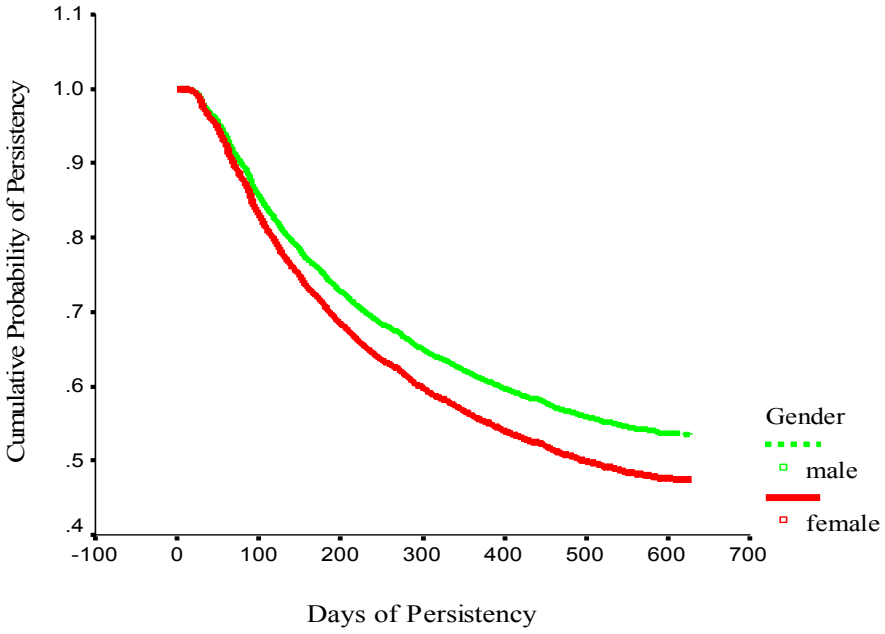


Figure A.2: Survival Function for Ethnicity Categories

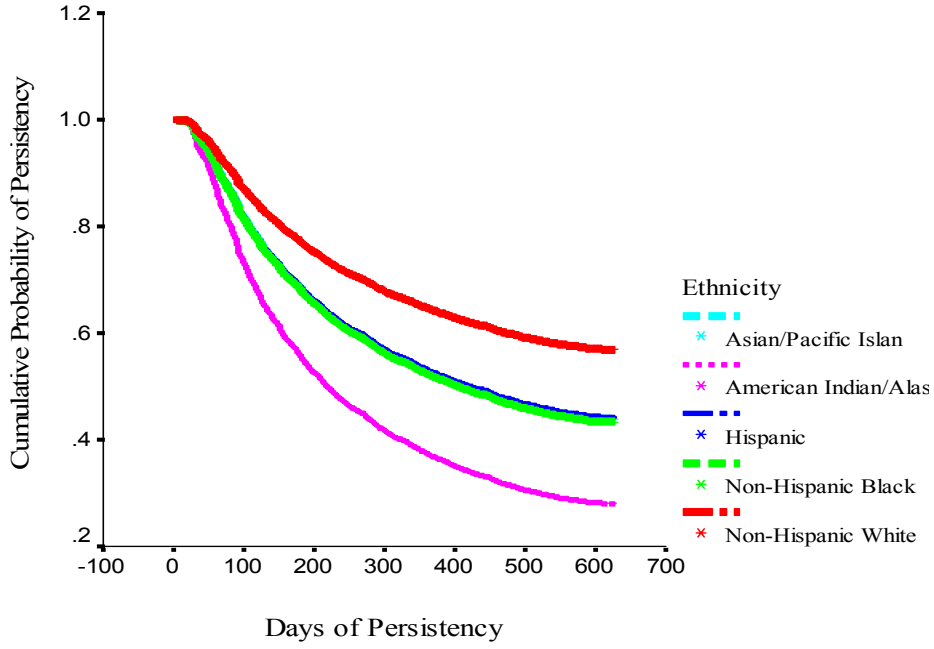


Figure A.3: Persistence Function for Diabetes Categories

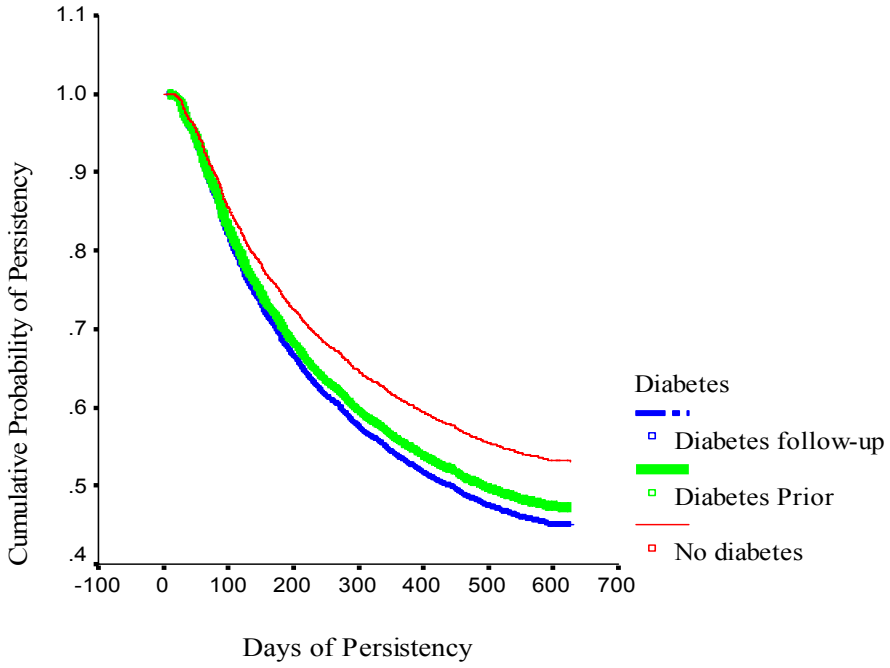


Figure A.4: Persistence Function for CHD Categories

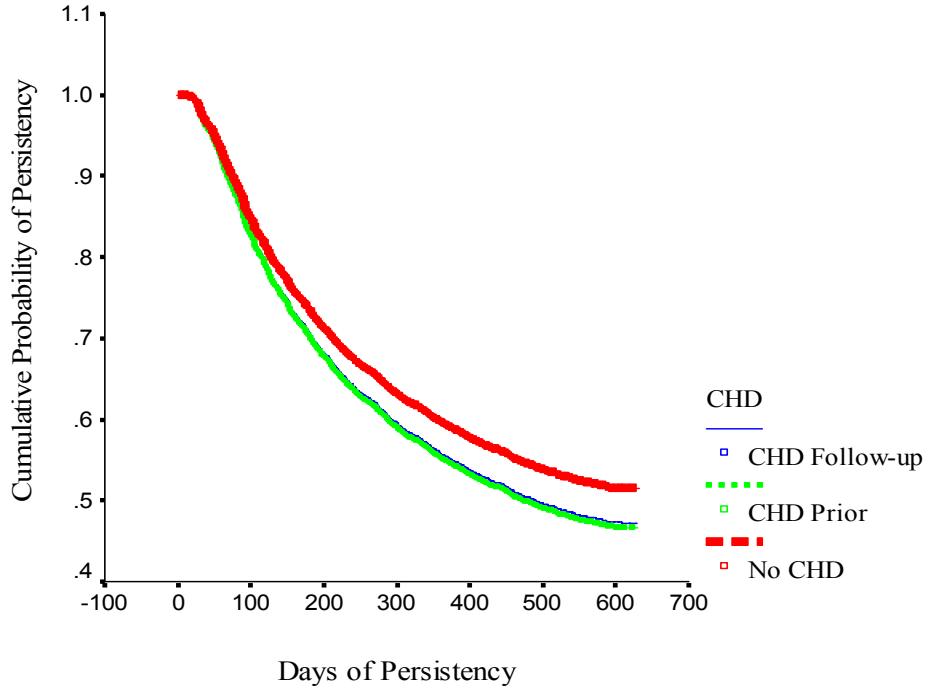


Figure A.5: Persistence Function for Hypertension Categories

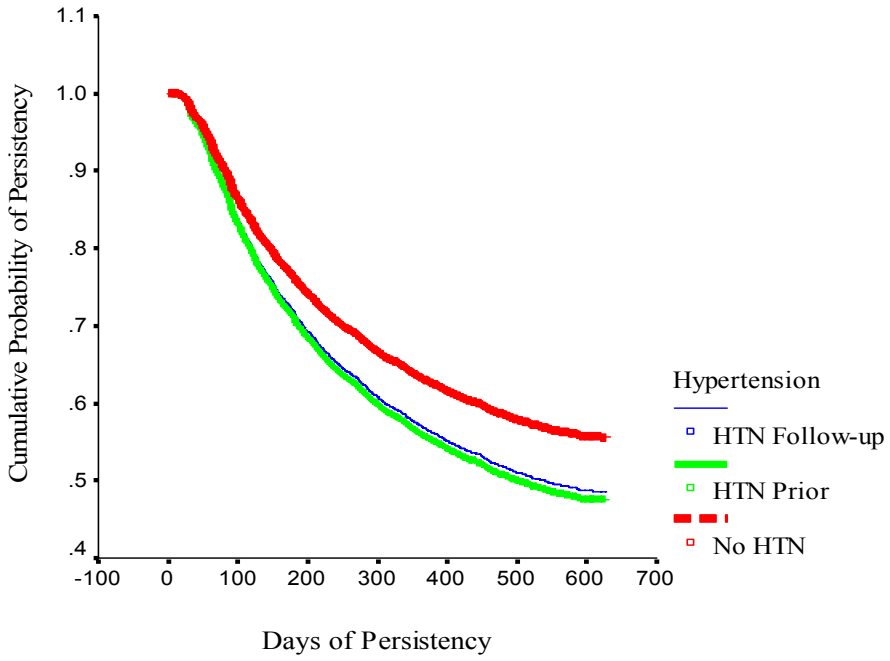
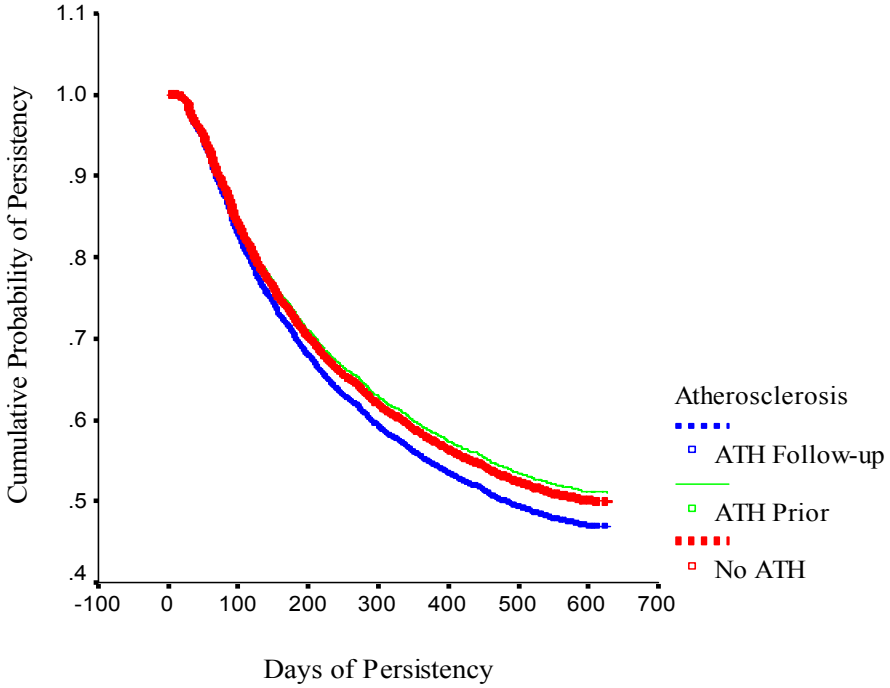


Figure A.6: Persistence Function for Atherosclerotic Disease Categories



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